ARCHIVES OF SURGERY

VOLUME 46 FEBRUARY 1943 NUMBER 2

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EFFECTS OF LOWERING TEMPERATURE OF AN INJURED EXTREMITY TO WHICH A TOURNIQUET HAS BEEN APPLIED

ALFRED BLALOCK, M.D.

BALTIMORE

In 10 experiments [1] performed recently in which a tourniquet was applied to a severely injured extremity for a five hour period and in which treatment consisted in the administration of blood plasma, it was found that death occurred in all instances and that the average period of survival was only fourteen hours. In 10 other experiments which were identical in execution, except that a tourniquet was not used, 8 animals recovered and the remaining 2 lived four and twelve days, respectively.

The present experiments were performed in order to determine the systemic effects of reducing the temperature of an injured extremity to which a tourniquet has been applied.

METHODS AND RESULTS

Procedure.—Large animals were used in all the experiments. Pain was prevented by the use of soluble pentobarbital U. S. P. (pentobarbital sodium) and morphine. Injury was caused by striking one of the posterior extremities many blows with a blunt instrument for five to eight minutes. A tourniquet was placed around the upper part of the injured thigh, and the extremity was surrounded by ice as soon as the traumatization was completed. The tourniquet was left in place for five hours. A total of 20 experiments was performed. In 10 of these, the intravenous administration of plasma was begun immediately after the tourniquet was removed. The total quantity of plasma injected corresponded to 5 per cent of the body weight of the recipient. With 2 exceptions, plasma was injected slowly over a five hour period. In the remaining 10 experiments no plasma was injected. In all the experiments the injured extremity was surrounded by ice for an eleven hour period.

Trauma; Tourniquet; Cold; Plasma.—Except for the cooling of the injured part, these experiments were performed in the same manner as those reported previously, in all of which the animals died. In the present experiments 5 of the 10 animals recovered.

From the Department of Surgery of the Johns Hopkins University and Hospital.

1. Duncan, G. W., and Blalock, A.: The Effects of the Application of a Tourniquet on the General Response to Gross Trauma to an Extremity, Surgery, to be published.

TABLE 1.—*The Effects of Trauma to the Leg, Application of a Tourniquet, Cooling of the Injured Part and Intravenous Injection of Blood Plasma*

Experiment Number	Dog, Weight, Kg.	Duration Tourniquet, Hours	Duration Ice Pack, Hours	Plasma Injected, Percentage of Body Weight	Hematocrit Reading			Temperature, Rectal, F.			Result	Survival Time, Hours	Regional Loss of Fluid, Percentage of Body Weight
					Control	5 Hours	10 Hours	Control	5 Hours	10 Hours			
1	7.5	5	11	5	47.0	40.0	25.0	102.8	97.4	84.2	Death	22	8.7
2	6.1	5	11	5	34.0	37.3	29.7	101.6	96.8	80.4	Recovery	..	...
3	6.2	5	11	5	41.7	44.5	35.5	101.7	95.4	88.2	Recovery	..	...
4	6.7	5	11	5	43.7	37.5	34.2	101.4	98.8	90.0	Recovery	..	...
5	9.2	5	11	5	48.3	44.4	38.0	102.3	96.1	84.0	Death	17	5.1
6	6.7	5	11	5	36.4	39.3	31.7	100.0	93.2	90.4	Recovery	..	...
7	5.7	5	11	5	47.0	44.8	30.7	101.4	93.8	87.4	Recovery	..	...
8	7.1	5	11	5	48.2	45.0	49.0	98.0	87.4	72.4	Death	17	3.5
9	10.1	5	11	5	37.2	43.8	34.8	103.2	96.0	77.5	Death	17	4.8
10	8.4	5	11	5	35.5	39.0	41.0	101.4	95.8	80.2	Death	15	5.1

TABLE 2.—*The Effects of Trauma to the Leg, Application of a Tourniquet and Cooling of the Injured Part (No Plasma Administered)*

Experiment Number	Dog, Weight, Kg.	Duration Tourniquet, Hours	Duration Ice Pack, Hours	Hematocrit Reading			Temperature, Rectal, F.			Result	Survival Time, Hours	Regional Loss of Fluid, Percentage of Body Weight
				Control	5 Hours	10 Hours	Control	5 Hours	10 Hours			
11	8.7	5	11	51.3	52.0	61.4	101.0	98.0	83.8	Death	26	3.9
12	8.8	5	11	31.8	34.4	33.7	103.0	99.3	89.4	Recovery	..	...
13	7.0	5	11	41.0	46.8	56.2	102.3	96.5	80.4	Recovery	..	...
14	6.7	5	11	39.0	52.0	54.3	102.2	95.0	....	Death	38	7.1
15	9.2	5	11	41.0	46.6	51.4	102.6	97.4	95.1	Death	19	5.2
16	10.3	5	11	44.6	40.4	50.0	101.8	93.2	83.0	Death	17	4.4
17	5.8	5	11	46.0	40.0	46.3	102.7	94.0	74.2	Death	21	6.5
18	9.4	5	11	40.8	36.4	51.2	98.4	90.2	78.4	Recovery	..	...
19	8.6	5	11	34.3	37.2	42.8	101.0	91.4	88.0	Recovery	..	...
20	8.6	5	11	43.6	52.4	57.7	102.5	97.8	88.2	Death	19	5.5

The alterations in the hematocrit readings were variable; a dilution occurred in the majority of the studies. A marked decline in the rectal temperature took place in all the experiments. This was undoubtedly due in part to the proximity to the rectum of the ice which was encasing the injured extremity. The decline in rectal temperature usually occurred more rapidly after the removal of the tourniquet. As stated previously, 5 of the 10 animals recovered. The survival period of the remaining 5 ranged from fifteen to twenty-two hours. The average loss of fluid into the injured part in these experiments equaled 5.4 per cent of the body weight. The results of these experiments are given in table 1.

Trauma; Tourniquet; Cold.—The other 10 experiments differed from those in the preceding group only in that the injection of blood plasma was not included. Four of the 10 animals recovered.

TABLE 3.—*Showing the Ill Effects of a Tourniquet and the Beneficial Effects of Lowering the Temperature of a Part Distal to a Tourniquet*

Experimental Procedures	Number of Experiments	Tourniquet Applied, Hours	Plasma Therapy, Percentage of Body Weight	Number of Animals Surviving	Average Survival Period of Remainder	Regional Fluid Loss, Percentage of Body Weight
Trauma; plasma therapy (no tourniquet)	10	0	5	5	8 days	....
Trauma; tourniquet; plasma therapy	10	5	5 to 10	0	14 hr.	7.8
Trauma; tourniquet; cold; plasma therapy	10	5	5	5	17 hr. 36 min.	5.42
Trauma; tourniquet; cold (no plasma)	10	5	0	4	23 hr. 20 min.	5.41

There was an increase in the hematocrit reading in most of the experiments and also a great decline in the rectal temperature. As stated, 4 of the 10 animals survived. The survival periods of the remaining 6 ranged from seventeen to thirty-eight hours, the average being approximately twenty-three hours. The average difference in the weights of the injured and of the noninjured parts in these experiments equaled 5.41 per cent of the body weight. The results of these studies are given in table 2.

COMMENT

In the previous experiments reported by Duncan and me it was noted that the application of a tourniquet to a severely traumatized extremity for a period of five hours greatly decreased the chances of survival of the animal. The present experiments show that cooling of the part distal to the tourniquet lessens the ill effects of shutting off and then releasing the blood supply to an injured part. The results

which were observed when the extremity distal to a tourniquet was cooled were almost as good as those noted when the application of ice was supplemented by the injection of plasma. The results of all these experiments are summarized in table 3.

These observations, as well as those reported previously on crush injuries,[2] indicate that the addition of local ischemia and anemia to trauma results in more deleterious effects than are caused by trauma alone. The general effects of trauma on the one hand and of trauma plus ischemia and anemia on the other may be very different. Furthermore, the present results, the previous experiments on crush injuries and the observations of Allen [3] and of Brooks and Duncan [4] indicate that the harmful effects of a tourniquet will be lessened if the temperature of the part distal to the constriction is lowered by suitable means. This may be due to a slowing of metabolic processes or to a number of other alterations.

The results of the experiments reported here indicate that the use of a tourniquet on an injured extremity should be avoided whenever possible, but that if some form of constriction is necessary the temperature of the distal ischemic and anemic part should if possible be lowered by artificial means.

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2. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, Ann. Surg. **115**:684, 1942; Shock Produced by Crush Injury: Effect of Administration of Plasma and Local Application of Cold, Arch. Surg. **45**: 183 (Aug.) 1942.

3. Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, Am. J. Surg. **45**:459, 1939.

4. Brooks, B., and Duncan, G. W.: Effects of Temperature on Survival of Anemic Tissue: Experimental Study, Ann. Surg. **12**:130, 1940.

DELETERIOUS EFFECTS OF ANOXIA ON THE LIVER OF THE HYPERTHYROID ANIMAL

MONROE A. McIVER, M.D.
AND
ELEANOR A. WINTER, M.A.
COOPERSTOWN, N. Y.

It has been recognized for some time that persons with thyrotoxicosis and animals in which a state of hyperthyroidism has been artificially produced are particularly sensitive to anoxia. The extraordinary sensitivity of thyroid-fed rats to want of oxygen was first brought out by Asher and Duran,[1] who showed that animals with hyperthyroidism did not tolerate even minor degrees of anoxia. The behavior picture presented by the rats in their experiments was characterized by dyspnea, unrest and convulsive movements; the animals finally became unable to move, were obviously dangerously ill and died unless air was given. Normal rats at the same oxygen tension were relatively unaffected. Streuli and Asher [2] had earlier found the converse to be true, namely, that thyroidectomized rats were able to tolerate a lack of oxygen which brought normal animals to the point of death by asphyxiation. In 1941 Barach and associates [3] confirmed the work of Streuli and Asher, demonstrating that after thyroidectomy rats show a remarkable increase in resistance to low oxygen tensions, such as those encountered in high altitudes. In their experiments the majority of thyroidectomized rats survived for three weeks in a chamber in which the oxygen was kept at 6 per cent (corresponding to an altitude of 31,500 feet [9.6 kilometers]), whereas normal rats kept in a similar atmosphere died in twelve to thirty-six hours.

In a survey of the literature no studies were found dealing particularly with the effects of anoxia on the liver during hyperthyroidism. That the

From the Surgical Research Laboratory, Mary Imogene Bassett Hospital.

1. Asher, L., and Duran, M.: Beiträge zur Physiologie der Drüsen: XLIV. Das Verhalten von normalen, mit Schilddrüsensubstanz gefütterten und schilddrüsenlosen Ratten gegen reinen Sauerstoffmangel, Biochem. Ztschr. **106**:254, 1920.

2. Streuli, H., and Asher, L.: Beiträge zur Physiologie der Drüsen: XXXVI. Das Verhalten von schilddrüsenlosen, milzlosen, schilddrüsen- und milzlosen Tieren bei O_2-Mangel, zugleich ein Beitrag zur Theorie der Bergkrankheit, Biochem. Ztschr. **87**:359, 1918.

3. Barach, A. L.; Eckman, M., and Molomut, N.: Modification of Resistance to Anoxia, with Especial Reference to High Altitude Flying, Am. J. M. Sc. **202**: 336, 1941.

liver in particular might suffer from want of oxygen seems reasonable. The cells of the liver are always nearer the point of asphyxiation than other cells of the body owing to the fact that only 25 per cent of their blood supply is arterial.[4] It may be assumed that the increased demands on the liver for oxygen during hyperthyroidism [5] leave a narrow margin of safety. Also, as shown in previous studies, the liver under conditions of hyperthyroidism is particularly susceptible to injury.[6]

The present paper records our experiments on the effect of anoxia on the liver during artificial hyperthyroidism.

METHOD AND MATERIALS

The experiments were carried out on male albino rats having an initial weight of between 150 and 175 Gm. The standard diet consisted of Purina dog chow, and in addition each rat was given 0.4 Gm. of yeast three times a week. Hyperthyroidism was produced by the subcutaneous injection of crystalline thyroxin [7] daily over a period of approximately two to three weeks in doses of 0.1 mg.

Autopsy was performed as soon as possible on animals that died, and blocks of tissue from the liver and other organs were fixed in Zenker's solution and in 1.6 per cent solution of formaldehyde. Animals that were killed were given a sharp blow at the base of the skull; autopsy was carried out immediately. When determinations of glycogen were to be carried out, the liver was removed within thirty seconds; a portion of the liver was immediately fixed in absolute alcohol for subsequent staining with Best's carmine, and the glycogen was determined according to the method of Good, Kramer and Somogyi.[8]

The apparatus used in the experiments on anoxia consisted of a bell jar 8 inches (20 cm.) in diameter and 12 inches (30.5 cm.) high set on a greased plate of ground glass and containing a wire gauze platform on which the rat was placed suspended over a pan of soda lime and calcium chloride. A two hole stopper at the top of the bell jar contained a thermometer and an exit tube. The bell jar was connected with a 40 liter spirometer which served as a reservoir for the gas mixtures used in the experiments. The mixtures were made by diluting room air in the spirometer with nitrogen until the desired percentage of oxygen was obtained. The gas mixture from the spirometer was run continuously through the bell jar. Samples of the mixture were drawn at frequent intervals from the

4. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, Williams & Wilkins Company, 1940, p. 468.

5. Reinwein, H., and Singer, W.: Studien über die Gewebsatmung: IV. Der Einfluss von Thyroxin, Adrenalin und Insulin auf den Sauerstoffverbrauch überlebender Leberzellen, Biochem. Ztschr. **197**:152, 1928.

6. (*a*) McIver, M. A.: Increased Susceptibility to Chloroform Poisoning Produced in the Albino Rat by Injection of Crystalline Thyroxin, Proc. Soc. Exper. Biol. & Med. **45**:201, 1940. (*b*) McIver, M. A., and Winter, E. A.: Further Studies on Increased Susceptibility to Chloroform Poisoning Produced in the Albino Rat by Injection of Crystalline Thyroxin, J. Clin. Investigation **21**:191, 1942.

7. The crystalline thyroxin for this work was supplied by E. R. Squibb & Sons, New York.

8. Good, C. A.; Kramer, H., and Somogyi, M.: The Determination of Glycogen, J. Biol. Chem. **100**:485, 1933.

exit tube and analyzed on a portable Haldane apparatus in order to check the concentration of oxygen.

The rats were placed singly in the bell jar and subjected for varying periods to the low concentrations of oxygen. In the early experiments the periods of exposure were short, both for controls and for thyroxin-treated rats, and occurred on successive days. In the later experiments slightly higher percentages of oxygen were in general used; the periods of exposure were considerably longer and were completed in one day.

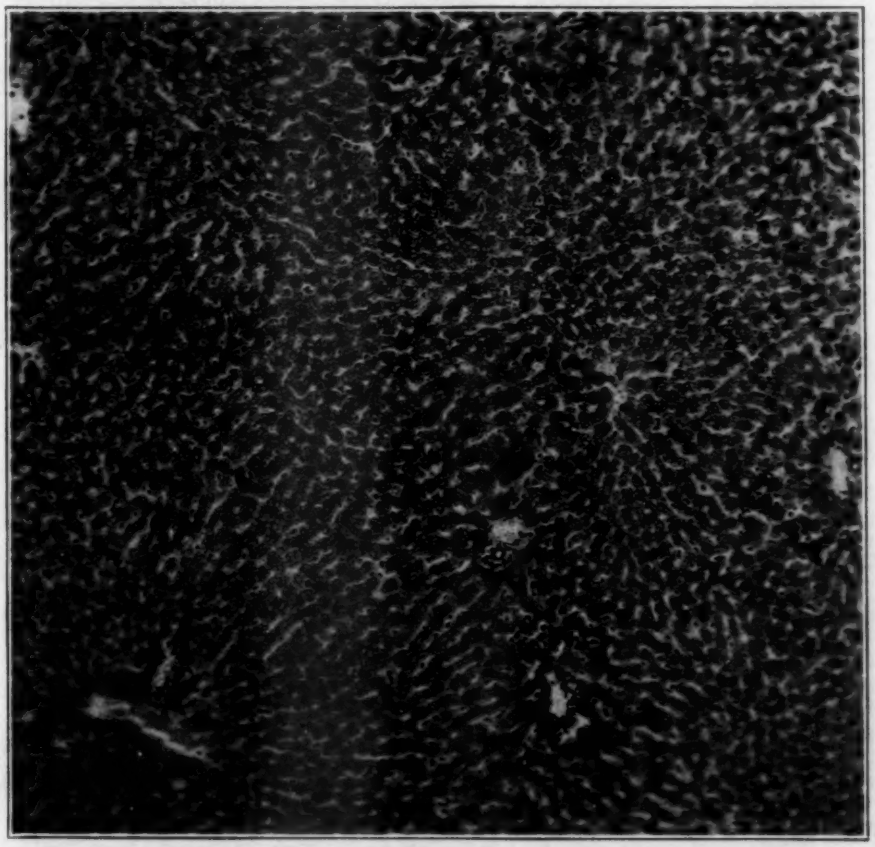

Fig. 1.—Section of the liver stained with hematoxylin and eosin, taken from control rat 6 after anoxia of nine and a half hours' duration. The concentration of oxygen was 11.2 per cent. There is no evidence of damage to the liver. (Magnification, × 100.)

PRELIMINARY OBSERVATIONS ON ANIMALS RECEIVING CRYSTALLINE THYROXIN

The various statements concerning thyroxin-treated rats are based on data acquired during the past two years on 186 rats.

The animals were usually kept for at least one week before the injections of thyroxin were started. This was done to make sure that they were all in healthy condition and to allow them to become adjusted to the laboratory environment. They were weighed three times a week, and their body temperatures were taken by rectum at the same time or in certain instances more frequently.

While the animals were receiving daily injections of thyroxin, they remained in general in good condition, as judged by appearance, state of the hair and activity.

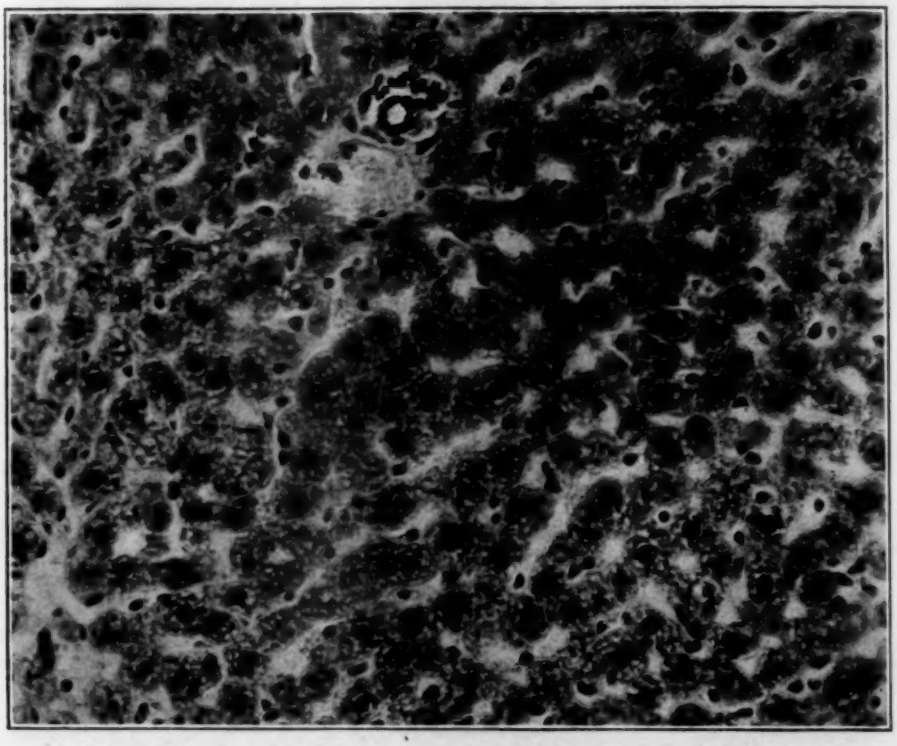

Fig. 2.—Higher magnification (× 300) of the section shown in figure 1.

Weight.—Control rats gained progressively throughout the period of observation, showing an average gain in weight of 2.6 Gm. per day. Approximately 70 per cent of the rats receiving crystalline thyroxin showed an initial drop in weight lasting from two to five days and amounting roughly to about 10 Gm. After this drop the weight was usually maintained until about the tenth day, from which time there was a slow gain. About 18 per cent gained weight slowly but continuously throughout the period of injections. The remaining 12 per cent had an erratic weight course, which is not readily classified.

Food Intake.—In the early stages of administration of thyroxin most of the rats showed a loss of appetite; during this stage they were frequently restless and mild diarrhea often developed. After the first week or ten days, however, the appetite returned and the amount of food consumed was greater than that taken by the controls.

Body Temperature.—The hyperthyroid rats frequently had a somewhat higher rectal temperature than the controls. Although there was

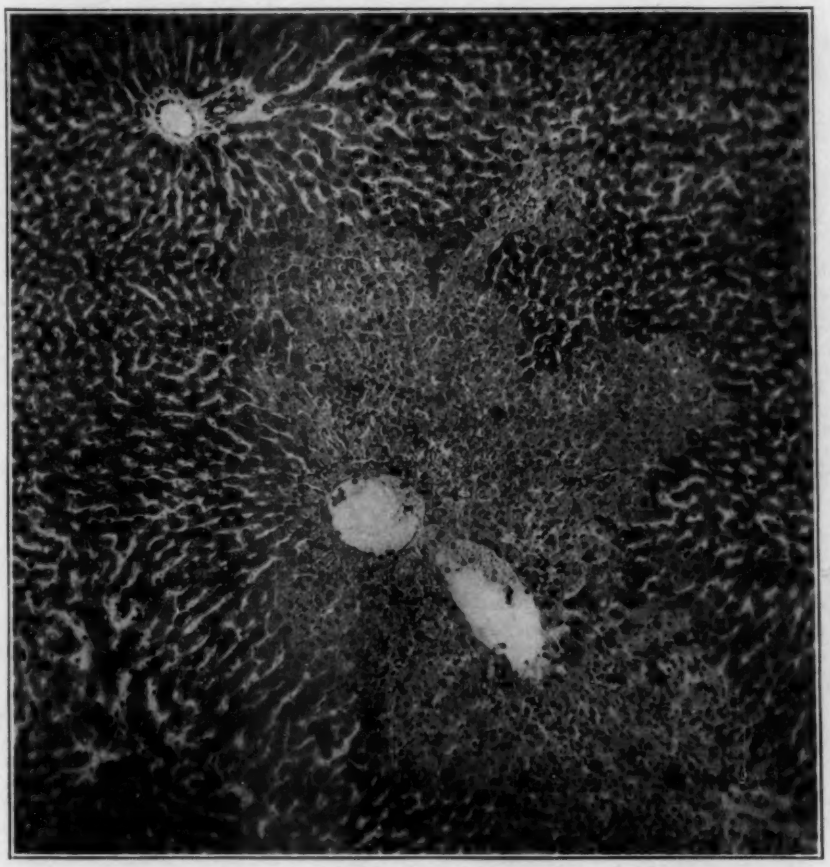

Fig. 3.—Section of the liver stained with hematoxylin and eosin, taken from rat 4, which went through a preliminary period of administration of thyroxin followed by anoxia of nine and a half hours' duration. The concentration of oxygen was 11.2 per cent. Areas of degeneration are shown. (Magnification, × 100.)

an average difference of only 0.3 C. (0.5 F.) in temperature between the two groups (that of the normal rats averaging 36.5 C. [97.7 F.] and that of the hyperthyroid rats 36.8 C. [98.2 F.]), none of the normal rats had a temperature as high as 37 C. (98.6 F.), whereas a number of the hyperthyroid rats had temperatures of 37 C. or slightly higher.

Hepatic Glycogen.—With the standard diet which we employed, the hepatic glycogen in control animals, as previously reported,[6b] varied from 7.1 to 5.0 Gm. per hundred cubic centimeters. In 39 thyroxin-treated rats on the same diet the glycogen level varied from 3.2 to 0.18 Gm. per hundred cubic centimeters, only 2 animals having a level above 1.6 Gm.

Histologic Examination of the Liver.—A study of the pathologic material from 31 rats that had been killed [9] after receiving injections of

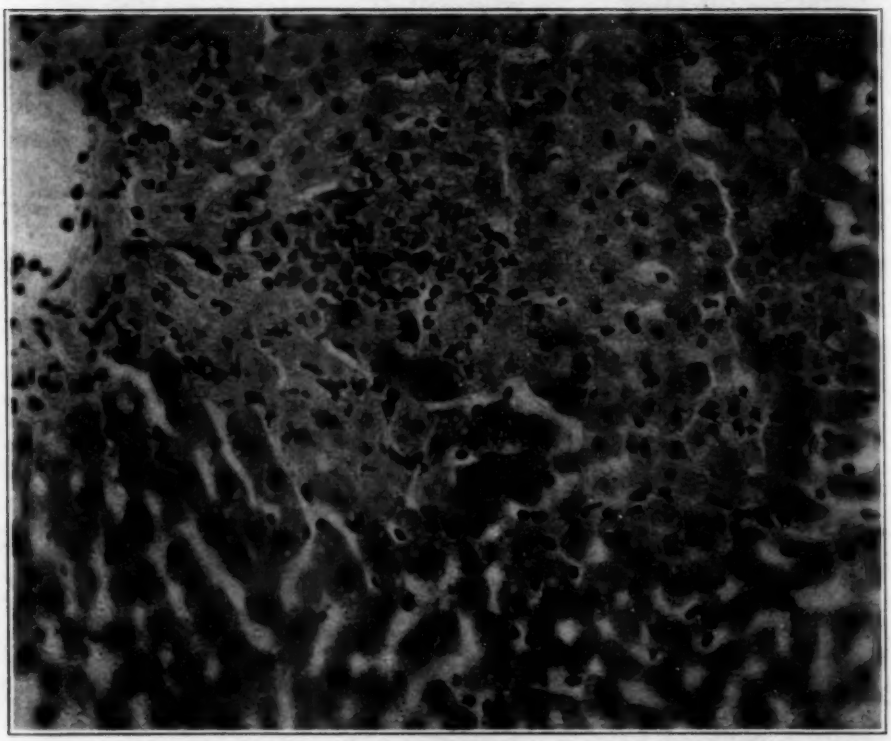

Fig. 4.—Higher magnification (× 300) of the section shown in figure 3. Note the boundary zone between the necrotic area and relatively normal hepatic tissue.

9. There are a number of studies in which histologic changes are said to have been produced in the liver by the administration of thyroxin. The studies in which these changes were noted, however, were carried out with the use of large or even fatal doses of thyroxin (Farrant, R.: Hyperthyroidism: Its Experimental Production in Animals, Brit. M. J. **2**:1363, 1913. Hashimoto, H.: The Heart in Experimental Hyperthyroidism with Special Reference to Its Histology, Endocrinology **5**:579, 1921. Gerlei, F.: Nécrose du foie consécutive à l'empoisonnement par la thyroxine, Ann. d'anat. path. **10**:555, 1933); in many cases these were given over long periods. An attempt was made in our experiments to use doses of

(Footnote continued on next page)

crystalline thyroxin over a period of approximately two to three weeks without exception failed to reveal any notable histologic abnormalities of the liver. Minor histologic differences were often found, however, when the cells were compared with those of the livers of normal well fed rats, the cells in the livers of thyroxin-treated rats being more homogeneous and compact. The appearance of these cells, however, did not

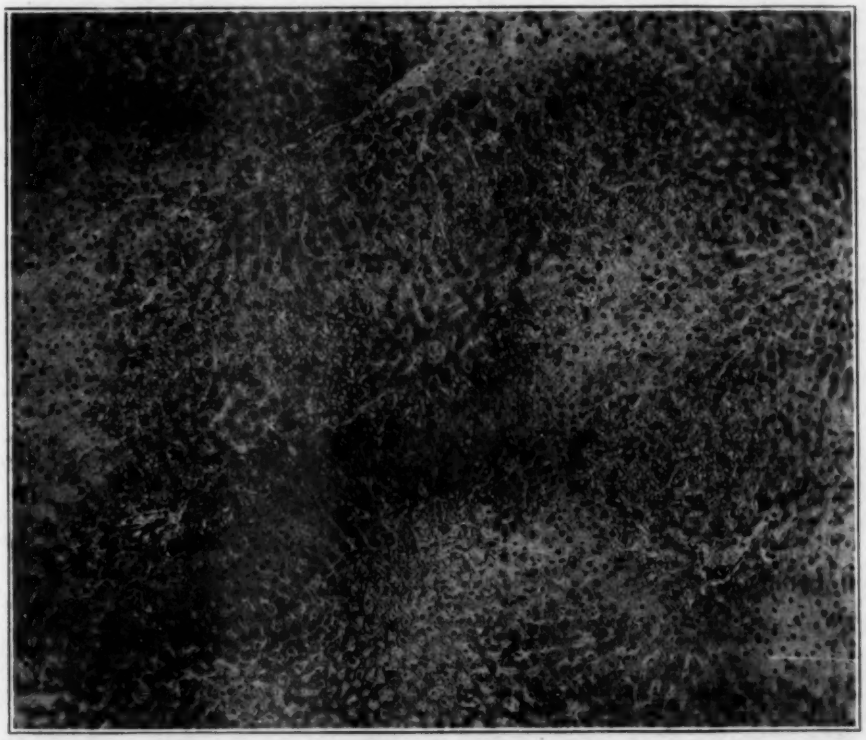

Fig. 5.—Section of the liver stained with hematoxylin and eosin, taken from rat 7, which went through a preliminary period of administration of thyroxin followed by anoxia of seven hours' duration. The concentration of oxygen was 11 per cent. Widespread necrosis of the liver is shown. (Magnification, × 100.)

thyroxin which while producing definite hyperthyroidism would not be lethal. With such doses and over the period in which we employed the drug, it seems clear that it produces no important histologic changes in the liver. During a period of two years there were 186 rats that received crystalline thyroxin, and among these 12 deaths occurred, usually ascribed to the effects of intercurrent infection, frequently of the respiratory tract. Histologic examination of the liver was carried out on 10 of these animals, and in 4 instances degenerative changes were found. It is interesting in this connection that G. Haban (Leberveränderungen bei experimentellem Hyperthyreoidismus, Beitr. z. path. Anat. u. z. allg. Path. **95**:573, 1935) in studying the effects of injections of crystalline thyroxin on the liver found important changes only when some intercurrent infection occurred.

differ particularly from that of hepatic cells of a starved animal and was probably due in both instances to the fact that the hepatic glycogen content was low.

OBSERVATIONS IN EXPERIMENTS ON ANOXIA

The behavior reaction of the hyperthyroid and of the normal animals when exposed to atmospheres containing approximately 11 per cent

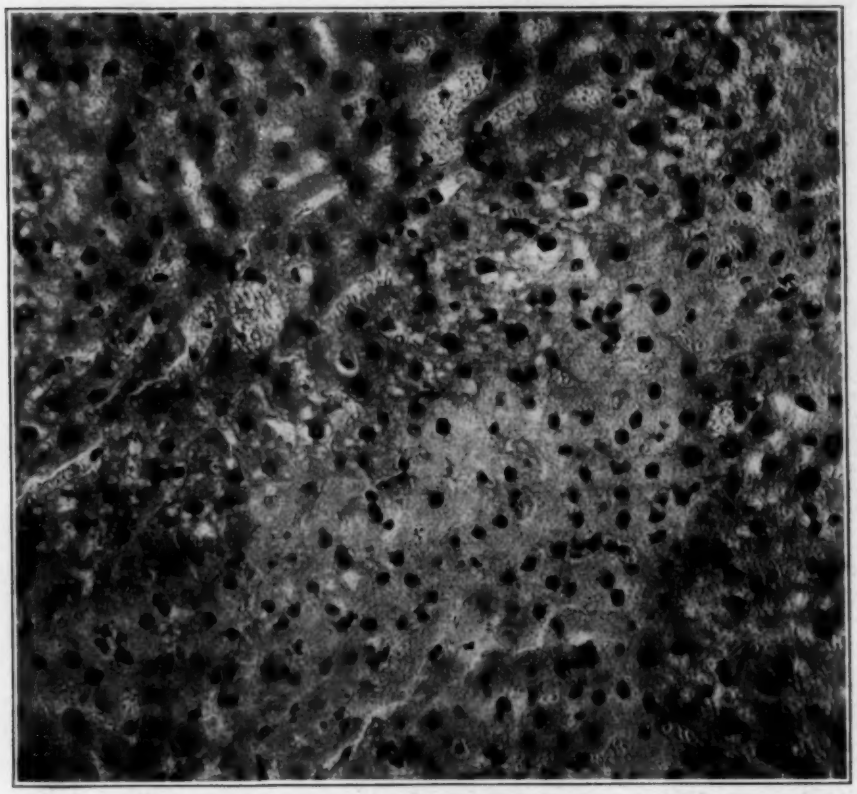

Fig. 6.—Higher magnification (× 300) of the section shown in figure 5.

oxygen in general showed marked differences. The normal animals for the most part slept quietly, and, although there was frequently some increase in their respiratory rate, they showed no signs of acute distress. The hyperthyroid animals, on the other hand, were restless and apathetic by turns. Their respiration became rapid and at irregular intervals was interrupted by a pause followed by a deep inspiration. They frequently assumed a position in which their heads were near the inlet of the bell jar. In general the behavior picture was similar to that described by Asher and Duran.[1]

The results of the experiments on anoxia are shown in tables 1 and 2. It will be noted that 26 rats were used; 17 of these had received injections of crystalline thyroxin over a period of approximately two to three weeks prior to being subjected to the low oxygen mixtures, while the 9 controls had received no thyroxin.

Mortality.—Nine of the 17 hyperthyroid rats died after varying periods of anoxia, which was in striking contrast to the absence of deaths

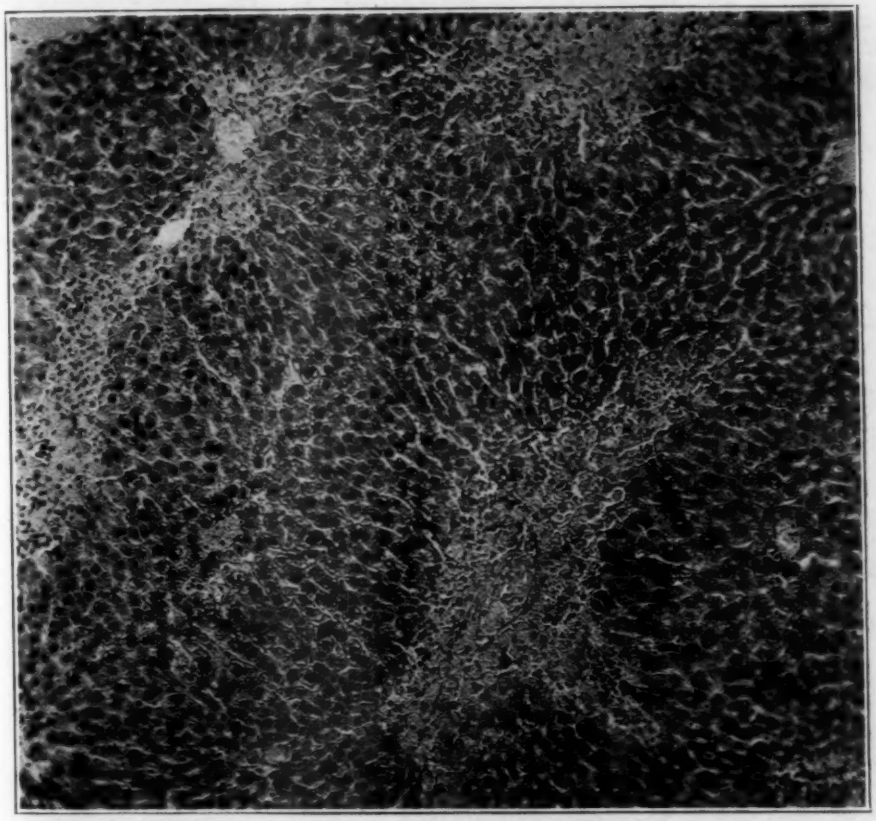

Fig. 7.—Section of the liver stained with hematoxylin and eosin, taken from rat 16, which went through a preliminary period of administration of thyroxin followed by anoxia of six and three-quarters hours' duration. The concentration of oxygen was 10.5 per cent. The animal was killed twenty-four hours after anoxia. Areas of degeneration are evident. (Magnification, × 100.)

among the 9 control rats similarly exposed to low oxygen atmospheres. The first two hours in the low oxygen atmosphere seemed to be the most critical for the hyperthyroid rats, and, although an attempt was made to return them to room air as soon as it was evident that their condition was becoming precarious, 5 of them died after this short exposure, 2

TABLE 1.—*Experiments on Anoxia with Hyperthyroid Animals* *

Rat	Administration of Crystalline Thyroxin: Total Amount, Mg.	Administration of Crystalline Thyroxin: Duration, Days	Anoxia: Oxygen, per Cent	Anoxia: Duration	Comment	Hepatic Glycogen, Gm. per 100 Cc.	Histologic Examination of Liver
1	1.8	18	9.3 9.5 10.0 10.3 6.5	56 min. 58 min. 80 min. 61 min. 65 min.	Killed 2 hr. 15 min. after removal from bell jar	0.8	No noteworthy deviation from normal
2	1.6	16	9.3 9.5 10.0	56 min. 58 min. 80 min.	Died after removal from jar in apnea; heart still beat, but respiration never resumed; autopsy done immediately	...	Marked engorgement of sinusoids; early degenerative changes in central portion of lobule
3	1.9	19	8.5 10.7 13.0	2 hr. 3 hr. 11 hr.	Near asphyxiation; limp but conscious; respiration moist; not disturbed by anoxia; killed immediately after removal from jar	...	No noteworthy degenerative changes seen
4	2.0	20	11.2	9½ hr.	Restless at times; respiration often jerky and irregular; seemed in good condition on removal from jar; killed 1 hr. later	...	Definite evidence of necrosis, most pronounced around central veins and spreading outward into lobule in irregular patterns; cells in areas of degeneration showed affinity for eosin; in some areas cell outlines completely lost
5	1.4	14	9.3	1⅔ hr.	Died in bell jar	...	Marked engorgement of sinusoids; early degenerative changes around central vein; cell outlines often lost; vacuoles in cytoplasm
6	2.7	27	12.5	1 hr.	Died in bell jar	...	Early changes
7	2.5	25	11.0	7 hr.	Respiration rate rapid; died in bell jar; autopsy done immediately	...	Widespread necrosis; large areas staining deeply with eosin; cell outlines in many places had disappeared; nuclei in these areas pyknotic
8	2.2	22	11.6	1 hr.	Died 6 hr. after removal from bell jar	...	Marked engorgement of sinusoids; early degenerative changes with loss of cell boundaries and pyknotic nuclei
9	1.6	16	11.0	9½ hr.	Killed 1 hr. after removal from jar	3.2	No outstanding deviation from normal
10	1.7	17	10.5	9½ hr.	Killed 1 hr. after removal from jar	0.5	Definite areas of degeneration; loss of cell boundaries; pyknotic nuclei and polymorphonuclear leukocytes seen among the necrotic cells
11	1.8	18	11.0	9½ hr.	Killed 1 hr. after removal from jar	3.1	Slight early degenerative changes
12	2.1	21	10.5	8 hr.	Died in bell jar	...	Extensive degeneration; marked engorgement of blood vessels; pyknotic nuclei; loss of cell boundaries
13	2.2	22	11.0	1 hr.	Died just after removal from jar	...	Marked engorgement of blood vessels; early degenerative changes with vacuolation of cells and loss of cell boundaries
14	2.4	24	10.0	8½ hr.	Died 5½ hr. after removal from jar	...	Extensive degeneration and hemorrhage
15	1.5	15	10.6	4 hr.	Died in bell jar	...	Marked engorgement of sinusoids and early degenerative changes
16	2.5	25	10.5	6¾ hr.	Stormy course; removed from bell jar early to prevent death; killed 24 hr. later	1.5	Extensive areas of degeneration and necrosis
17	1.6	16	11.0	8½ hr.	Killed 24 hr. after removal from jar	1.0	Widespread degenerative changes and necrosis

* Among the 17 animals with hyperthyroidism 14 showed evidence of hepatic damage varying from slight early changes to extensive necrosis. There were 9 deaths among these animals.

before they could be removed from the bell jar, 2 shortly after removal and 1 six hours later. The 4 other deaths occurred after varying periods of anoxia.

Pathologic Examination of the Liver.—With 2 exceptions the animals killed were put to death about an hour after termination of the anoxia.

The control rats without exception showed no lesions of the liver (table 2). Fourteen of the 17 hyperthyroid rats had such lesions. As might be expected, the lesions in animals that died or were killed after

TABLE 2.—*Experiments on Anoxia with Normal Rats* *

Control Rat	Anoxia: Oxygen, per Cent	Anoxia: Duration	Comment	Hepatic Glycogen, Gm. per 100 Cc.	Histologic Examination of Liver
1	11.0 9.3 5.9 8.7 8.7	40 min. 38 min. 50 min. 42 min. 37 min.	Killed 1½ hr. after removal from bell jar	2.5	No essential deviation from normal
2	11.0 9.3 5.9 8.7 8.7	40 min. 38 min. 50 min. 42 min. 37 min.	Killed 1½ hr. after removal from bell jar	....	No essential deviation from normal
3	7.5	7.5 hr.	Lethargic but not especially distressed; not killed		
4	11.2	9½ hr.	Killed 1 hr. after removal from bell jar	3.2	No essential deviation from normal
5	11.5 11.2	6 hr. 9½ hr.	Killed 1 hr. after removal from bell jar	...	No essential deviation from normal
6	11.2	9½ hr.	Killed 1 hr. after removal from bell jar	4.4	No essential deviation from normal
7	11.3	9½ hr.	Killed 1 hr. after removal from bell jar	3.5	No essential deviation from normal
8	11.2	9½ hr.	Killed 1 hr. after removal from bell jar	4.7	No essential deviation from normal
9	11.5	9½ hr.	Slept quietly throughout; killed 1 hr. after removal from bell jar	2.7	No essential deviation from normal

* There were no deaths among the 9 control rats, and examination of the liver revealed no degenerative changes.

short exposures were not advanced; they consisted of fatty changes, vacuolation of cells and engorgement of blood vessels.[10] In the animals exposed for longer periods the degenerative changes were usually severe and widespread. Outstanding lesions of the liver are shown in figures 3 to 10 and may be contrasted with the normal hepatic cells of a control animal shown in figures 1 and 2. In 2 instances the rats were killed twenty-four hours after being removed from the bell jar, and the lesions

10. As stated previously, in some of the earlier experiments both controls and thyroxin-treated animals were killed after short exposures. Since the changes in the thyroxin-treated rats were slight, longer periods of anoxia were used in later experiments.

of the liver found in 1 of them (rat 16) are shown in figures 7 and 8. This animal, as shown in table 1, tolerated the low oxygen atmosphere poorly and had to be removed after approximately seven hours. The general condition for several hours thereafter was not satisfactory, the animal appeared weak and the respiration was rapid. The next morning, however, the condition seemed essentially normal.

Fig. 8.—Higher magnification (× 300) of the section shown in figure 7, presenting the area of degeneration in detail.

Hepatic Glycogen.—Lewis and associates,[11] in their recent studies on the role of the adrenal cortex in acute anoxia, confirmed the earlier work of Evans,[12] showing that hepatic glycogen tends to increase in rats

11. Lewis, R. A.; Thorn, G. W.; Koepf, G. F., and Dorrance, S. S.: The Rôle of the Adrenal Cortex in Acute Anoxia, J. Clin. Investigation **21**:33, 1942.

12. Evans, G.: The Effect of Low Atmospheric Pressure on the Glycogen Content of the Rat, Am. J. Physiol. **110**:273, 1934; The Adrenal Cortex and Endogenous Carbohydrate Formation, ibid. **114**:297, 1936.

exposed to low atmospheric pressure. Lewis and his co-workers noted, however, that prior to this increase, during the first twelve hours of exposure to low concentrations of oxygen, there is a fall in the glycogen level. Our periods of anoxia all came within the twelve hour period, and as might be expected in view of the observation of Lewis and his associates, the glycogen level in these rats, both thyroxin-treated and normal animals, was low. It is interesting that although our controls and

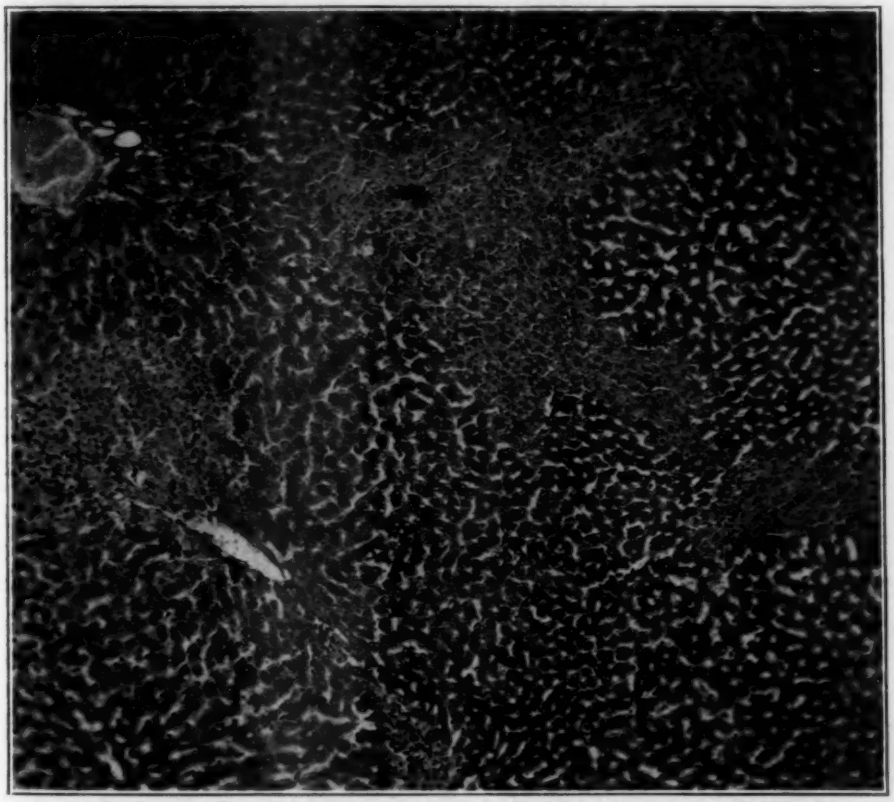

Fig. 9.—Section of the liver stained with hematoxylin and eosin, taken from rat 10, which went through a preliminary period of administration of thyroxin followed by anoxia of nine and a half hours' duration. The concentration of oxygen was 10.5 per cent. Numerous areas of necrosis are shown. (Magnification, × 100.)

our hyperthyroid animals both showed low levels of hepatic glycogen, damage to the liver occurred only in the latter group. This is in harmony with recently published observations by us,[6b] which showed that the low level of hepatic glycogen in hyperthyroid rats was not the essential factor in their increased susceptibility to chloroform poisoning.

Body Temperature.—In the control animals during exposure to anoxia there was a drop in body temperature averaging 2.2 C. (4 F.). The rats with hyperthyroidism similarly exposed showed in most instances some drop in temperature; this averaged 1.2 C. (2.2 F.), or a degree (C.) less than the drop in the controls. In 4 of the hyperthyroid animals there was a slight rise in body temperature, of about 0.5 C. (0.9 F.), and in 1 there was a rise of 1.8 C. (3.2 F.). In the 2 hyperthyroid animals

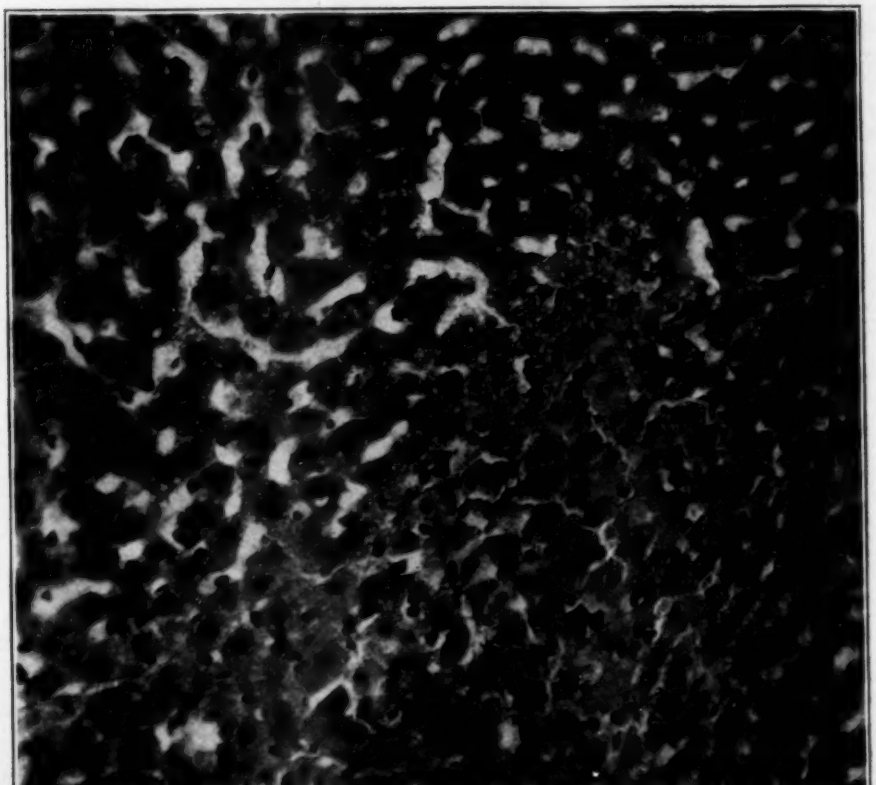

Fig. 10.—Higher magnification (× 300) of the section shown in figure 9, presenting one area of degeneration in greater detail.

that were not killed until twenty-four hours after removal from the bell jar, there was a slight rise in temperature after the termination of the anoxia.

COMMENT

On the basis of these experiments it seems evident that anoxia is capable of producing degenerative changes in the liver in animals with hyperthyroidism; this finding may in some instances explain the acute

lesions found in the livers of patients dying of hyperthyroidism.[13] The problem is of clinical importance, since anoxia is a hazard to which hyperthyroid patients are often exposed.[14] This is especially true after operations on the thyroid gland, when tracheal obstruction, pulmonary edema or some other complication may interfere with efficient aeration of the lungs. Also, according to Hartman,[15] hyperpyrexia, a constant feature of the thyroid crisis, may in itself contribute to anoxia.

SUMMARY

Rats given injections of crystalline thyroxin for two to three weeks in doses of 0.1 mg. daily in general remained in good condition, although they showed clinical signs of hyperthyroidism and when they were killed the hepatic glycogen level was found to be low. They showed no degenerative lesions of the liver.

On exposure to atmospheres containing low concentrations of oxygen, in 14 of 17 hyperthyroid animals varying degrees of hepatic injury developed. There were 9 deaths among the total of 17 rats.

In a group of control normal rats similarly exposed to low concentrations of oxygen hepatic lesions did not develop. There were no deaths in this group.

It is suggested that in some instances the acute lesions found in the livers of patients dying of hyperthyroidism may be the result of anoxia.

32 Fair Street.

13. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter, Ann. Int. Med. **7**:543, 1933. Beaver, D. C., and Pemberton, J. deJ.: The Pathologic Anatomy of the Liver in Exophthalmic Goiter, ibid. **7**:687, 1933. Shaffer, J. M.: Disease of the Liver in Hyperthyroidism, Arch. Path. **29**:20 (Jan.) 1940. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, M. Clin. North America **6**:445, 1922. Lichtman, S. S.: Liver Function in Hyperthyroidism, with Special Reference to the Galactose Tolerance Test, Ann. Int. Med. **14**:1199, 1941. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test: II. Thyroid Disease, Arch. Surg. **37**:427 (Sept.) 1938.

14. Haines, S. F., and Boothby, W. M.: Oxygen Treatment with Special Reference to Treatment of Complications Incident to Goiter, Am. J. Surg. **7**:174, 1929. Schnedorf, J. G.; McClure, R. D., and McGraw, A. B.: Rationale and Use of Oxygen in the Postoperative Treatment of Hyperthyroidism, Surg., Gynec. & Obst. **72**:26, 1941. Cole, W. H., and Brunner, R.: Anesthesia in Thyroidectomy for Thyrotoxicosis, ibid. **70**:211, 1940.

15. Hartman, F. W.: Lesions of the Brain Following Fever Therapy: Etiology and Pathogenesis, J. A. M. A. **109**:2116 (Dec. 25) 1937.

DELAYED SPLENIC RUPTURE: A CLINICAL SYNDROME FOLLOWING TRAUMA

REPORT OF FOUR CASES WITH AN ANALYSIS OF ONE HUNDRED AND SEVENTY-SEVEN CASES COLLECTED FROM THE LITERATURE

EDWARD J. ZABINSKI, M.D.
AND
HENRY N. HARKINS, M.D., PH.D.
DETROIT

Acute conditions within the abdomen remain among the most important and at the same time most complicated of all surgical syndromes. In the present state of war interest in traumatic injuries is increased, with good reason. The type of acute abdominal injury to be discussed in this paper has not received the attention that its frequency warrants. This syndrome differs from other examples of acute abdominal conditions in that a latent period varying from a matter of hours to days or even weeks may follow the original trauma. During this latent period the patient may complain of an associated injury, such as a fracture of a long bone or a rib; he may be troubled by vague abdominal pain, or he may actually be almost symptom free. Then in typical cases a gradually developing splenic hematoma suddenly ruptures and the patient presents signs of collapse, shock and severe anemia; if operation is not promptly performed, he dies. This condition, with its original injury, insidious latent period and fulminating secondary hemorrhage, is the condition of delayed splenic rupture.

Injury to the spleen is probably the most common of all serious subcutaneous abdominal injuries. Bronaugh (1935) reported that injury to the spleen occurs in 33.3 per cent of subcutaneous injuries involving abdominal viscera. Mazel (1932) reported a frequency of 30 per cent, and Wright and Prigot (1939) found the incidence to be 47.6 per cent. Injury to the liver was next in frequency, with a 28.6 per cent incidence. Trauma accounts for rupture of the normal spleen in almost every case. It may be caused by falls and from automobile, motorcycle and bicycle accidents, as well as by other types of violence. Accidents occurring in aeroplanes and in swiftly moving tanks may cause splenic rupture in wartime.

Delayed splenic rupture accounts for a far higher percentage of all splenic lacerations than is commonly realized. Thus it is seen in

From the Division of General Surgery, Henry Ford Hospital.

table 1 that from 5 to 40 per cent of all ruptures are of the delayed type, the average incidence being 14 per cent. Since McIndoe's review in 1932, sporadic reports have cited the infrequency of this condition. In reality the ratio of delayed to immediate hemorrhage is about 1 to 6. Werthmann, of Frankfort on the Main, Germany, had 4 cases in two years, while Orator (1939) saw 2 examples of the syndrome in Schmieden's clinic in one year. In this condition there is the advantage —seldom utilized as yet—that during the latent period operation may be performed, or at least the condition diagnosed and the patient observed expectantly. Splenic hemorrhage, immediate or delayed, is rapidly fatal

TABLE 1.—*Ratio of Delayed to Total Splenic Ruptures in Reported Series*

Author	Year	Splenic Ruptures		Delayed Ruptures as Percentage of Total Cases
		Delayed	Total	
Bailey (London Hospital)	1894-1926	6	32	19
Connors	1928	3	32	9
Foster and Prey	1940	1	20	5
Rousselot and Illyne	1941	1	17	6
Zabinski and Harkins	1942	4	10	40
Total		15	111	14

TABLE 2.—*Collected Series of Cases of Delayed Splenic Rupture*

Author	Year	Number of Cases
Nast-Kolb	1912	9
Schlegel	1926	16
Herfarth	1926	25
Quénu	1926	22
Kment	1930	42
Becker	1932	45
McIndoe	1932	46
Werthmann	1932	52
Hageney	1939	70
Müller	1940	75
Zabinski and Harkins	1942	177

unless immediate operation is performed, and is therefore one of the gravest abdominal emergencies requiring surgical intervention.

ANALYSIS OF LITERATURE

Since no other review has included more than 40 per cent of the reported cases, it was felt that a collective study of this important syndrome was in order. In 1912 Nast-Kolb collected 9 cases of delayed splenic rupture. Other reviews are shown in table 2. Data on the following cases are not available: Séjournet, 1933; Popoviciu and Mihaileanu, 1933; Bronaugh, 1935; Dorronsoro Montes, 1936; Mashtakov, 1936; Bergan, 1939; Vasilkovan, 1939; Krivonosov, 1939; Montanari, 1941 (2 cases); Monod, 1931, and Spiridonovič, 1932.

The present analysis is based on 66 new cases collected from the literature as well as 4 cases of patients treated at the Henry Ford Hospital. Our cases are divided under the following heads: cases 1 to 46, cited by McIndoe (1932); cases 47 to 80, additional cases cited by Müller (1940); cases 81 to 107, incomplete or untraceable reports; cases 108 to 111, 4 personal cases; cases 112 to 177, 66 previously uncited cases collected from the literature.

Cases 1 to 46.—The review by McIndoe (1932) represents the most complete report on delayed splenic rupture which has appeared in the English language up to the present time. The discussion of cases therein is so complete that we have not reanalyzed them in the present paper.

Cases 47 to 80.—Müller (1940) collected 80 cases of delayed splenic rupture from the literature. Three of these are duplications, and 2 of them (those of Herfarth and of Stamm) are doubtful. This article, however, with its 75 definite cases, still represents the most extensive review outside of our own. Thirty-four of Müller's cases are not included in our own series or are not cited by McIndoe. They include those of Abasbridze, Becker, Borchard, Brogsitter, Burgerhout, Cadénat, Fuchs, Gohrbandt, Haffter, Henderson, Heuser, Hochwalter, Junkermann, Kauff, Kofranek (2 cases), Ledderhose, Mannheim, Marx, Mastador, Molnár, Moore and Alexander, Monod, Patey, Ramon, Rolle, Roughton, Schachnowitz, Schmidt, Schubert, Soison, Stefanini, Turnagallie and Wildanker.

Cases 81 to 107.—These represent reports with data insufficient for analysis, or for which the reference could not be checked. In this list are 27 cases, including those of Bailey (1927), 5 cases; Bergan (1939), Bronaugh (1935), Connors (1928), 3 cases; Dorronsoro Montes (1936), Kempf (1923), Krivonosov (1939), Mashtakov (1936), Monod (1931), Montanari (1941), 2 cases; Pietrzikowski (1920), Popoviciu and Mihaileanu (1933), Pou, 2 cases; Rousselot and Illyne (1941), Séjournet (1933), Spiridonovič (1932), Vasilkovan (1939), Wiederkov (1920) and Zubkov.

Cases 108 to 177.—These include the cases of 4 patients seen at the Henry Ford Hospital and 66 additional cases collected from the literature. None of the latter are included in McIndoe's report. These 70 cases form the chief basis for our analysis and are listed hereinafter.

PERSONALLY OBSERVED CASES

Case 108.—W. C., a man aged 36, was struck with a milk bottle in the region of the left kidney. Two days later he had some abdominal pain, relieved by a bowel movement. Six days after the injury the patient was seized with a severe pain in the left shoulder, with collapse and generalized severe abdominal pain. He vomited a small amount. The temperature, the pulse and the respirations were normal.

Findings included tenderness in the upper part of the abdomen and a white blood cell count of 12,200. A preoperative diagnosis of pancreatitis or perforated peptic ulcer was made. At operation the abdomen was found to be filled with blood. A 3 cm. laceration on the diaphragmatic surface of the spleen was felt. Splenectomy was done, and recovery ensued.

CASE 109.—C. McM., a man aged 43, was struck over the left shoulder and knocked down by a barrel falling 14 feet (4.25 meters). He felt weak momentarily. It was found that he had a fracture of the eighth rib on the left side in the mid-axillary line. For the next few days his temperature rose to 101 F. No cause for the fever could be found. Five days after the initial injury, while straining at the stool, he began to feel weak and perspired profusely. In five hours the patient was blanched and had pain only over the site of the fracture. There was no abdominal pain or tenderness. The hemoglobin content dropped from 14.6 to 11.8 Gm. per hundred cubic centimeters. A diagnosis of intra-abdominal hemorrhage was confirmed at operation, at which time a fragmented spleen was removed. The patient was pulseless during the splenectomy but responded to blood transfusions. He left the hospital in good condition.

CASE 110.—O. L., a man aged 49, was admitted to the hospital one day after an automobile-train wreck. He presented marked splinting of the entire abdomen, especially in the lower half. There was also tenderness in the region of the left kidney. The blood pressure was 120 systolic and 68 diastolic. The pulse and the temperature were normal. During the next few days the abdomen became softer, although it always maintained slight rigidity. Seven days after the injury severe abdominal pain, cold sweat, pallor and delirium developed. The blood pressure was not obtainable. The pulse rate was 130, and the temperature was normal. The patient received 1,000 cc. of blood, and splenectomy was done. On the second postoperative day bronchopneumonia developed, and the patient died on the third day after operation.

CASE 111.[1]—O. M., a man aged 48, had an automobile accident on Nov. 18, 1940, after which he remained in bed because he felt tired. During this time he had a little abdominal pain on the left side. Four and one-half days after the injury he became suddenly gravely ill, with collapse, weak pulse and fall in blood pressure. The white blood cell count was 20,700, and the hemoglobin content was 11.5 Gm. per hundred cubic centimeters. Abdominal exploration was done at once by one of us (H. N. H.). Free blood was present in the peritoneal cavity, associated with a 2.5 cm. laceration of the splenic capsule and a hematoma under the capsule at the site of rupture. Splenectomy was done, and the patient was given a transfusion during the operation. Postoperatively bronchoscopic examination was made for aspiration pneumonia, and thrombophlebitis developed in the right leg, for which continuous injection of heparin was used. The patient was discharged from the hospital in good condition.

REPORTED CASES

A series of 66 reported cases of traumatic subcutaneous rupture of the spleen with delayed hemorrhage is presented and forms an essential element of the statistical analysis later in this article. The following facts are tabulated: author, date of the report, age of the patient, sex, initial injury, latent period, type of onset of secondary

1. This case has previously been reported *in extenso* by one of us (H. N. H.).

hemorrhage, symptoms, signs, associated lesions, pathologic changes, result, complications, preoperative diagnosis and comment. Cases on which data are insufficient or not obtainable have been mentioned on the previous pages. The cases reviewed by McIndoe (1932) are not included in this list, which represents reports with details adequate for analysis.

CASE 112 (Richardson, 1923).—The patient, a boy aged 12 years, fell off a bicycle. Six days later he had pain in the left side of the abdomen and the left shoulder with sudden onset. Operation revealed a ruptured spleen with much free blood in the peritoneal cavity. Splenectomy was followed by recovery.

CASE 113 (Heymann, 1927).—After an automobile accident, a physician suffered abdominal pain, which rapidly improved. Nine days later he had pain in the shoulder and the abdomen with sudden onset. Operation revealed a tear at the hilus of the spleen; this organ, however, was not removed because of shock. Death ensued.

CASE 114 (Bailey, 1927).—A workingman aged 40 was hit in the upper part of the abdomen by a pole. He fainted but soon recovered sufficiently to report to the hospital, where he was examined and told to report the next day. This he did not do, because he felt better. Five days later he suffered sudden collapse with evident signs of internal hemorrhage; splenectomy was done a few hours later with recovery.

CASE 115 (Martens, 1927).—A physician received an injury in a motorcycle accident. Two days later he had abdominal pain, distention and rigidity. A diagnosis of peritonitis was made, and at operation the lower third of the spleen was found to be torn off. An accessory spleen was also removed. The patient recovered.

CASE 116 (Wilson, 1927).—A man aged 55 was struck by a falling log. He had no pain in the abdomen after the second day. Nine days after the accident abdominal pain developed, but there was no tenderness and no rigidity. The temperature was normal; the pulse rate was 100. The patient died in thirteen hours without benefit of operation. Autopsy revealed rupture of an infarct of the spleen and amyloid degeneration of the liver.

CASE 117 (Nelson, 1928).—A man aged 61 was thrown against a wall by a cow. He was treated for fractured ribs. Thirteen hours later he became pale. The pulse rate was 120, and there was dulness in both flanks. The spleen was ruptured, and splenectomy for tears at the hilus and the costal surfaces was done. The patient recovered.

CASE 118 (Berndt, 1929).—A woman aged 23 was struck in the left upper quadrant of the abdomen by her husband. Thirteen days later the patient had gradual onset of two attacks of abdominal pain and dizziness. Pallor and tenderness in the left hypochondrium were noted. The temperature was 37.5 C. (99.5 F). The pulse was weak, and the rate was 125. There was intra-abdominal bleeding, and splenectomy was done; a 2 cm. tear near the hilus was discovered at operation. The patient recovered.

CASE 119 (Kment, 1930).—A man aged 21 was hit in the left side of the abdomen. Fifty hours later there was sudden onset of abdominal pain and pain in the left shoulder, associated with vomiting and collapse. The abdomen was rigid and tender, and a diagnosis of splenic rupture was made. At operation 1.5

liters of blood was found in the abdominal cavity; there was a rupture of the splenic capsule. Recovery took place after splenectomy.

CASE 120 (Kment, 1930).—A man aged 25 was in an automobile accident. He was admitted to the hospital, and his condition improved. However, on the tenth day in the hospital he had rapid onset of pain in the abdomen and left shoulder, accompanied by vomiting. The abdomen was tender, distended and boardlike. There was dulness in the flanks. Operation revealed a splenic rupture and tear of the capsule. The patient recovered after splenectomy.

CASE 121 (Dawson-Walker, 1931).—A woman aged 34 received a blow to the left side of the back. Two weeks later the patient experienced gradual onset of severe epigastric pain and pain in the shoulder. No collapse took place. There was no pallor, no shifting dulness in the flanks and no rigidity. The temperature was 97.6 F., the pulse rate 120, and the respiratory rate 28. The patient was operated on and was found to have internal hemorrhage from a ruptured subcapsular hematoma. Death from shock occurred the first day after splenectomy.

CASE 122 (Hochmiller, 1931).—A man aged 22 fell flat on his back. Twenty-four hours later pain in the abdomen developed, associated with weakness, nausea, collapse, anemia, distention and shifting dulness. The temperature was 37.7 C. (99.86 F.) and the pulse rate 120. A diagnosis of ruptured liver or spleen was made. There was laceration of the capsule, and splenectomy was followed by a wound infection. Recovery occurred. A blood count taken one year later was entirely normal.

CASE 123 (Wagner, 1931).—A man aged 25 was struck with a hammer in the left hypochondrium. Two days later he complained of pain in the abdomen. There was no collapse. Dulness was present in the upper part of the abdomen. The temperature was 37 C. (98.6 F.). A diagnosis of ruptured peptic ulcer was made, and a hilar laceration was found at operation. Recovery took place after splenectomy.

CASE 124 (Bumm, 1931).—A woman aged 23 fell downstairs twice. Twelve days later she had to remain in bed one day. Forty-one days after the accident abdominal pain and shock developed rapidly, and the patient vomited. She was pulseless and had a distended and tender abdomen. Anemia was present. The presence of blood on vaginal puncture led to the diagnosis of a ruptured ectopic pregnancy. Operation revealed a subcapsular hematoma and tear of the entire convex surface of the spleen. The patient recovered.

CASE 125 (Oudard and Guichard, 1932).—A man aged 30 fell into a dry-dock. Four days later he experienced generalized abdominal pain, tenderness and rigidity in the left hypochondrium. Dulness was present in the left flank. The temperature was 38.6 C. (101.48 F.), and the pulse rate was 100. The patient was operated on, and intraperitoneal hemorrhage, probably splenic, was discovered. A subcapsular and perisplenic hematoma was found. The patient died of anuria due to a transfusion reaction.

CASE 126 (Oudard and Guichard, 1932).—A youth aged 20 fell off a bicycle. Twenty-four hours later pain in the left shoulder, epigastrium and left hypochondrium développed, associated with tenderness and rigidity. A splenic rupture was diagnosed and a subcapsular hematoma was found at operation. The patient recovered.

CASE 127 (Oudard and Guichard, 1932).—A boy aged 16 fell 4 meters and suffered a fracture of a rib on the left side and of the right radius and a transverse rupture of the spleen. Forty hours later pain developed in the upper part

of the abdomen and collapse occurred. There was subcostal rigidity and tenderness, low blood pressure and dulness in the splenic area. The temperature was normal, and the pulse rate was 90. The patient recovered after splenectomy.

CASE 128 (Oudard and Guichard, 1932).—A youth aged 20 was struck by an assailant's fist under the left costal margin. Five hours later subcostal pain and collapse developed, with rigidity. The temperature and the pulse were normal. At operation a subcapsular hemorrhage with no free blood in the peritoneal cavity was found. Recovery ensued.

CASE 129 (Kohn, 1932).—A man aged 48 fell while drunk. On the fifth day colicky abdominal pain developed, associated with nausea, pallor, abdominal distention and tenderness. The temperature was 37.3 C. (99.14 F.), and the pulse was weak. A diagnosis of acute appendicitis was made. At operation a 4 cm. capsular tear of the spleen was discovered, and there was 1,000 cc. of blood in the peritoneal cavity. The patient recovered after operation. Bronchitis was a complication in this case.

CASE 130 (Werthmann, 1932).—A boy aged 13 fell while ice-skating. Eight hours later extreme pallor, and restlessness developed. The patient was operated on, and a tear of the convexity of the spleen was found. He recovered.

CASE 131 (Werthmann, 1932).—A man aged 31 was involved in a motorcycle accident. Twenty-seven hours later extreme pallor developed, and there was dulness in the left upper quadrant of the abdomen but no distention. When the patient was operated on the spleen was found to be in three parts, and there was a hematoma of the mesentery. The patient recovered after operation.

CASE 132 (Werthmann, 1932).—A girl aged 4 was run over by an automobile. Forty-six hours later acute abdominal pain developed, associated with dulness and tenderness in the left upper quadrant of the abdomen. There was a fracture of the humerus. On operation two lacerations of the spleen were noted; these divided the spleen into three parts. The patient recovered after operation.

CASE 133 (Werthmann, 1932).—A woman aged 29 was in a motorcycle accident. Ninety hours later she experienced abdominal pain and vomiting. Examination revealed dulness in the left side of the abdomen and pallor. A tear of the convexity of the spleen was discovered at operation. The patient recovered.

CASE 134 (Bertrand, 1933).—A youth aged 18 was involved in a motorcycle accident. He had slight abdominal pain, but thirty-six hours later severe abdominal pain developed, associated with syncope, sweating and extreme pallor, but there was no abdominal tenderness. The pulse rate was 160. Operation revealed an intraperitoneal hemorrhage. The spleen was in two pieces, one being in the pelvis. Recovery occurred in spite of pulmonary complications.

CASE 135 (Kirschner, 1933).—A man aged 28 fell 2.5 meters, fracturing the left ulna. Hematuria developed, and eight days later, while straining at the stool, he experienced pain in the left upper quadrant of the abdomen and collapsed. The hemoglobin content of the blood was 80 per cent. The pulse was poor. Operation revealed a splenic rupture, a 6 cm. tear of the convexity and 1,500 cc. of blood in the peritoneal cavity. The patient recovered.

CASE 136 (Modezejewski, 1933).—A woman aged 26 fell downstairs. She remained in bed only three days. On the twelfth day after the accident sudden collapse developed, with abdominal pain and rigidity, vomiting, a pulse rate of 136, and a temperature of 35.8 C. Operation revealed a capsular tear of the spleen with a subcapsular hematoma. Splenectomy was followed by recovery.

CASE 137 (Dodd, 1934).—A man bumped his left lower ribs during a fall. After a free interval of twelve hours severe pain in the upper part of the abdomen, with vomiting and diarrhea, began to develop. The temperature was 100 F. and the pulse rate 120, and there was tenderness over the cecum; hence a diagnosis of acute appendicitis was made. The operation, which required only fifteen minutes, was accompanied by shock and revealed a laminated perisplenic hematoma. Splenectomy was followed by recovery.

CASE 138 (Dodd, 1934).—A woman aged 56 struck her chest on a chair during a fall. She continued to do her housework, although she did not feel well. Two days later, with a slow onset, abdominal pain, weakness and dyspnea developed. Shifting dulness in the flanks and rigidity, tenderness and dulness in the left upper quadrant of the abdomen were noted. The temperature was 99 F., the pulse rate 120 and the hemoglobin content of the blood 55 per cent. A diagnosis of ruptured spleen was made. Operation was accompanied by shock and revealed a laceration of the spleen. Splenectomy was followed by recovery.

CASE 139 (Meltzer, 1935).—A young man fell 4 meters. Two days later he became ill suddenly, with pain in the upper part of the abdomen, and collapse ensued. Operation revealed a splenic rupture. Splenectomy was followed by recovery.

CASE 140 (Moulonguet and Suire, 1935).—A man aged 37 fell off a motorcycle. A basal fracture of the skull was diagnosed. He had abdominal tenderness for a few days. After nine days pain in the left upper quadrant of the abdomen, pain in the left shoulder and shock developed. There was dulness in both flanks, and the pulse rate was 180. The patient was operated on, and internal hemorrhage and a subcapsular splenic hematoma were revealed. Splenectomy was done, and the patient recovered.

CASE 141 (Hunter, 1935).—A man aged 33 fell from a motorcycle on his abdomen and left shoulder. A progressively enlarging abdomen, making the patient unable to walk, became apparent. There was severe abdominal pain, and anemia and fluid waves were noted. The peritoneal cavity was explored twenty days after the accident, and 9 pints (4.25 liters) of fluid blood was removed; the spleen was not removed because bleeding had ceased.

CASE 142 (Gardiner, 1935).—A youth aged 19 fell from a fence. He remained in bed for six days, during which time he had only one bowel movement. On the seventh day at breakfast the patient was seized with severe abdominal pain and pain in both shoulders and with faintness. The temperature was 97 F., and the pulse rate was 92. Rigidity and tenderness over the abdomen were noted, and there was increased splenic dulness. There was a laceration of the long axis. Splenectomy was done, and the patient recovered.

CASE 143 (Schmid, 1935).—A woman aged 38 fell and struck the left splenic region. Twenty-eight days later, while washing clothes, she became suddenly sick, with severe abdominal pain, and collapse occurred. A fractured left rib was discovered. There was a question of a tubal pregnancy in this case. Splenectomy was performed for a subcapsular hematoma, and recovery took place.

CASE 144 (Wenger, 1936).—A girl aged 19 fell down a flight of stairs. She had pain on standing straight, pain in the upper part of the abdomen and weakness. Seven days after the accident the patient suddenly went into collapse and had pain in the left side of the abdomen and left shoulder. Shifting dulness, and fluid waves were noted. The temperature was 99.6 F., and the pulse rate was 144. She was treated for a broken rib. The diagnosis of a probable ruptured

spleen was made. At operation a rupture of the anterior surface was found, for which splenectomy was done. Because of the shortness of the splenic pedicle a portion of the tail of the pancreas had to be included in the ligature. Recovery ensued.

CASE 145 (Sertoli, 1936).—A man aged 49 was hit by a motorcycle. There was slight contracture of the abdomen the first few days, but on the ninth day the patient became gravely ill with generalized abdominal pain, collapse, anemia and generalized rigidity. The pulse rate was 100. The diagnosis of a perforated gastric ulcer was made. At operation a large splenic laceration was found, and splenectomy was done. The patient died.

CASE 146 (Laporte, 1936).—A man aged 35 was struck and pinned under a car. He vomited after the accident. After two days sharp pain developed in the left hypochondrium and he went into sudden collapse. The pulse rate was 120. A ruptured spleen was found at operation, and there were 4 liters of blood in the peritoneal cavity and a tear near the hilus. The patient died in shock after the operation.

CASE 147 (Laporte, 1936).—A man aged 32 suffered a fall. Two days later sharp periumbilical pain and pain in the left shoulder suddenly developed, associated with nausea and tenderness and dulness in the splenic region. The pulse rate was 100. A ruptured spleen was revealed on operation, and there was 1.5 liters of blood in the abdominal cavity. A subcapsular hematoma was present. Recovery took place after operation.

CASE 148 (Mouchet and Léger, 1936).—A man aged 32 fell from a roof. Three days later he had sudden pain in the left upper quadrant of the abdomen, pain in the shoulder and nausea, followed by collapse. There were tenderness and rigidity in the left upper quadrant of the abdomen and slight distention. The temperature was 37.6 C. (99.68 F.), and the pulse rate was 120. There were a fractured eleventh rib and a left hemothorax. A ruptured spleen was diagnosed. Subcapsular hemorrhage and tear of the diaphragmatic surface of the organ were discovered at operation, and there was 1.5 liters of free blood in the peritoneal cavity. Phlebitis developed, but the patient eventually recovered.

CASE 149 (De Monie, 1937).—A youth aged 20 fell off a motorcycle, striking the left side of his chest and flank. Two days later the patient went into sudden collapse, with vomiting, low blood pressure, pain in the epigastrium and left shoulder and tenderness in the epigastrium and left hypochondrium, which in twenty-one hours became localized in the left upper quadrant of the abdomen. There was dulness in the region of the liver and the left iliac fossa. The temperature was 37.2 C. (98.96 F.) and the pulse rate 120. A ruptured spleen with subcapsular hematoma and a hilar tear was found at operation. Splenectomy was followed by recovery.

CASE 150 (Bonfield, 1937).—A man aged 27 was in an automobile that was struck by a streetcar. He appeared pale after the accident. Two days later he went into collapse, with severe abdominal pain, chiefly in the left hypochondrium. The spleen was found to be ruptured and was three times its normal size. A subcapsular hematoma and a tear in the convexity of the spleen were found. Postoperatively the hemoglobin content of the blood was 60 per cent and the white cell count 43,000. The patient recovered.

CASE 151 (Hohenwallner, 1938).—A man aged 55 had a fall and was hospitalized for five days. Four months later he became suddenly sick with abdominal pain. Pallor and abdominal dulness, distention and tenderness were noted on exam-

ination. A diagnosis of perforated peptic ulcer was made. There was a tear of the upper pole of the spleen 3 cm. deep. The patient had had malaria twenty years previously. He recovered after operation.

Case 152 (Lange, 1938).—A man aged 45 was hit in the left side of the abdomen. Pleurisy developed, followed on the fourth day by cold sweats and pain in the left shoulder and abdomen, associated with rigidity and tenderness. A ruptured spleen was found at operation. After a follow-up period of nine months recovery was considered complete.

Case 153 (Wright and Prigot, 1939).—A woman aged 36 was in an automobile accident. She had pain in the left upper quadrant of the abdomen for a few days. Two weeks later there was a sudden onset of pain in the left side of the chest and the left shoulder, with nausea and fainting. The blood pressure was 90 systolic and 74 diastolic. The red cell count of the blood was 2,900,000, the hemoglobin content 65 per cent and the white cell count 6,100. The patient was short of breath. An abdominal tap revealed blood. A diagnosis of acute pancreatitis was made. A ruptured spleen was discovered at operation. Splenectomy was followed by recovery.

Case 154 (Wright and Prigot, 1939).—A woman aged 22 sustained a fracture of the eighth rib on the left side in an automobile accident. The patient had recurrent symptoms indicative of slow onset of hemorrhage. Two weeks after the accident pain in the left side of the chest and left shoulder and general malaise developed. After three days she again became asymptomatic, remaining so until the day before her admission to the hospital, three weeks after the accident. At the time of her admission the hemoglobin content of the blood was 45 per cent, the red cell count 2,700,000 and the white cell count 21,300. The temperature, pulse and respirations were normal. The original diagnosis of pneumonia was changed to that of splenic rupture because of abdominal symptoms of increasing severity. Splenectomy was performed, and the patient recovered.

Case 155 (Blocker, 1939).—A man aged 34 felt a sharp evanescent pain in the left upper quadrant of the abdomen while lifting a heavy beam. One and one-half days later, while at the stool, the patient was seized with pain in the left flank. Pallor and generalized abdominal tenderness were noted. The blood pressure was 90 systolic and 60 diastolic, and the pulse rate was 128. There was dulness in both flanks. A diagnosis of probable ruptured spleen was made. The spleen was found hanging from the pedicle by a few shreds of capsule, and a subcapsular hematoma was present. Recovery took place after operation.

Case 156 (Delannoy, 1939).—A man aged 45 fell off a bicycle. After the accident he had slight persistent pain in the left upper quadrant of the abdomen. On the eighth day, on arising from bed, he was suddenly seized with a sharp pain in the left upper quadrant and collapsed. There were tenderness and abdominal distention. The temperature was 37.9 C. (100.22 F.) and the pulse rate 90. There were ecchymoses at the umbilicus. At operation a ruptured spleen with laceration of the superior pole and parenchymatous hemorrhage was found. There was 1.5 liters of blood in the abdomen. The patient recovered after splenectomy.

Case 157 (Webb, 1939).—A boy aged 8 years was struck by a puck during a hockey game. On the fourth day, while he was putting on his coat, pain in the left side and classic symptoms of ruptured spleen suddenly developed. At operation a laceration of the outer surface and two subcapsular hematomas were found. The patient recovered after splenectomy.

CASE 158 (Orator, 1939).—A youth aged 17 was hit in the left upper quadrant of the abdomen. Eight days later he was suddenly seized with abdominal pain, associated with shock, weakness, pallor and a hemoglobin content of 50 per cent. Operation disclosed an intra-abdominal hemorrhage. Splenectomy was performed, and recovery ensued.

CASE 159 (Orator, 1939).—A man aged 38 was struck in the left upper quadrant of the abdomen in an automobile accident. He was asymptomatic until three days later, when some abdominal pain developed. On the fifth day the pain suddenly became worse, so that he was unable to stand up. The hemoglobin content of the blood was 70 per cent and the white cell count 17,000, and there was tenderness in the left upper quadrant of the abdomen. A diagnosis of splenic rupture was made. Operation revealed that the capsule was separated from the entire convex surface of the spleen and that there was 1,500 cc. of free blood in the peritoneal cavity. Splenectomy was followed by recovery.

CASE 160 (Kufferath, 1939).—A woman aged 24 walked to the hospital after being hit in the left upper quadrant of the abdomen. She had pain in the back and a slow onset of symptoms of internal hemorrhage. At operation 1,500 cc. of free blood was removed. The patient recovered after splenectomy.

CASE 161 (Segal and Jaffe, 1939).—A woman aged 42 fell downstairs but continued with her housework until the twelfth day after the accident, when she suffered increasing pain in the left side of the abdomen associated with vomiting. Within twenty-four hours the patient was in shock. The blood pressure was 50 systolic and 0 diastolic. The hemoglobin content of the blood fell from 62 to 42 per cent and the red cell count from 3,400,000 to 2,900,000. The white cell count was 12,200. The pulse rate ranged from 100 to 130. At operation a ruptured spleen with a tear of the capsule and tamponade by clots was found. Splenectomy was done, and the patient recovered.

CASE 162 (Piulachs, 1939).—A man aged 46 fell 12 feet (3.65 meters). On the twelfth day pain in the shoulder, collapse, pallor and swelling below the ribs developed over a period of seven hours. The temperature was 37.5 C., and the pulse rate was 100. A cyst of the spleen was found on operation, and there were hemorrhage and fragmentation. A laceration of the kidney was also revealed. The patient died.

CASE 163 (Zschau, 1939).—A man aged 30 was hit by a motorcycle on the left side. He had some pain on the left side on expiration, and his left elbow was fractured. Seven days after the accident rapid collapse occurred, accompanied with abdominal pain. Operation revealed a 6 cm. tear in the spleen, with infarction and with 750 cc. of free blood in the peritoneal cavity. Splenectomy was followed by recovery.

CASE 164 (Foster and Prey, 1940).—A boy aged 13 tripped over a fence, striking his chest and abdomen. He had no immediate symptoms other than mild colic. On the third day he was seized with pain in the left side of the abdomen and vomited. Examination revealed dulness in the left flank, with rigidity. The hemoglobin content of the blood was 80 per cent, the red cell count 3,500,000 and the white cell count 12,500. The temperature was 99.6 F., and the pulse rate was 85. A diagnosis of delayed splenic rupture was made. At operation bleeding of the superior pole of the spleen was found, and tamponade was done. A wound disruption with secondary hemorrhage and an intestinal obstruction necessitated two additional operations, but the patient eventually recovered.

CASE 165 (Puestow, 1940).—A man aged 43 fell 102 feet (31 meters). He fractured eight ribs on the left side, the first lumbar vertebra, the left tibia and the left os calcis. There was slight rigidity in the left upper quadrant of the abdomen. On the fifteenth day he was suddenly seized with severe pain in the left upper quadrant of the abdomen and left side of the chest. Collapse ensued, and abdominal rigidity and tenderness were noted. The pulse rate was 140. At operation intra-abdominal hemorrhage, probably splenic, was discovered. There was also a subcapsular hemorrhage, and the pedicle of the spleen was torn. The patient recovered after splenectomy.

CASE 166 (Steenrod, 1940).—A lineman aged 20 fell 30 feet (9.4 meters) after contact with a live wire. He was severely burned and suffered a fracture of the tenth rib on the left side, with pneumothorax. Nine days later severe epigastric pain developed, accompanied with vomiting and collapse. The blood pressure was 70 systolic and 0 diastolic. Fluid waves were noted in the abdomen. The temperature was 99.6 F., and the pulse rate was 128. A spleen enlarged to three times its normal size and a tear of the lower pole of the spleen were found at operation. Evisceration with obstruction in the splenic fossa subsequently developed, and the patient died on the twenty-ninth day.

CASE 167 (Cheeves, 1940).—A youth aged 17 sustanied an injury while playing football. He presented slowly developing, recurrent symptoms of splenic rupture and after two days went into shock. At operation a subcapsular hematoma and a large laceration across the middle of the spleen were found. Splenectomy was followed by recovery.

CASE 168 (Davis, 1940).—A woman aged 38 was in an automobile accident. She received a blow over the left side of the chest, followed by pain in the left upper quadrant of the abdomen and the left shoulder. Four days later she had an attack of generalized abdominal pain, felt nauseated and collapsed. The pulse rate was 132. The blood pressure was 118 systolic and 78 diastolic, the hemoglobin content of the blood 25 per cent and the white cell count 12,600. There was general abdominal tenderness, with dulness in both flanks. The spleen was found to be disrupted on operation. The patient died ten hours postoperatively.

CASE 169 (Müller, 1940).—A railroad engineer aged 40 was struck on the left side when his bicycle fell on top of him, but was able to go to work. Six hours later he went into a state of collapse, with pain, tenderness and rigidity in the left upper abdominal quadrant. The white cell count of the blood was 15,200 and the hemoglobin content 85 per cent, and there were signs of fluid in the abdomen. Operation revealed a tear in the splenic capsule with coagula in the substance of the organ. Splenectomy was followed by pneumonia and death on the fifth day.

CASE 170 (Müller, 1940).—A laborer aged 38 was well for thirty-six hours after a fall. With a slow onset over a twelve hour period abdominal pain developed, accompanied with tenderness in the left upper quadrant of the abdomen, pallor and weakness. The temperature was 38 C. (100.4 F.), the white blood cell count 18,000 and the blood pressure 120 systolic and 85 diastolic. A diagnosis of acute appendicitis preceded operation. A tear at the hilus of the spleen with free blood in the peritoneal cavity was found. Splenectomy was followed by evisceration and peritonitis, and death occurred on the eighth day.

CASE 171 (Müller, 1940).—A woman aged 40 fell downstairs, striking the left side very hard. Except for occasional pain in the shoulder she was well for two years, after which abdominal pain, weakness and tenderness in the left upper quadrant of the abdomen suddenly developed. A diagnosis of peritonitis led to

operation, at which free blood was found in the peritoneal cavity coming from a thick-walled hemorrhagic cyst in the left upper quadrant of the abdomen and attached to the spleen. Splenectomy led to recovery.

CASE 172 (Deaver, 1941).—A man aged 24 suffered fractures of the nose, left scapula, left clavicle and left third and fourth ribs when an automobile in which he was riding overturned. There was transient pain in the left upper quadrant of the abdomen. On the twenty-third day severe abdominal pain suddenly developed, followed by collapse. Slight anemia, abdominal tenderness and fluid waves were noted. The temperature was normal, and the pulse rate was 108. Roentgenograms showed elevation of the left dome of the diaphragm. Splenectomy revealed that the anterior surface of the spleen was torn. The patient recovered.

CASE 173 (Frank, 1941).—A youth aged 17 was injured while playing football. He had no definite complaints until two days later, when pain in the left side of the abdomen and left shoulder developed, followed by collapse. On his admission to the hospital the temperature was 100 F. and the pulse rate varied from 80 to 90. At operation an intra-abdominal hemorrhage was revealed. The spleen was torn completely through, the tear extending into the splenic pedicle. The patient recovered.

CASE 174 (Fey and Turow, 1941).—A man aged 50 was struck over the left side of the chest in a fight. On the sixth day pain in the epigastrium and the left shoulder developed, and the patient vomited. Eight hours later he went into shock. No attempt was made to elicit Ballance's sign. The temperature was 96 F., and the pulse was feeble. The pulse rate was 140; the respiratory rate, 36. At operation a subcapsular rupture of the spleen was found. The patient recovered.

CASE 175 (Lommen, 1942).—On June 6, 1936 a boy aged 14 collided with another boy while chasing a ball, the other boy's head striking him in the abdomen. He was at once brought to the hospital. The red blood cell count was normal; the white cell count, 18,600. There were some generalized abdominal pain and tenderness. Two days after the accident the patient was discharged with a diagnosis of contusion of the spleen, and three days later he returned to school. On June 13, seven days after the accident, abdominal pain, tenderness and rigidity, especially in the left upper quadrant, suddenly developed, accompanied with faintness, sweating, pallor and a compressible pulse. A splenectomy, performed at once after a blood transfusion, revealed a laceration 7 cm. long in the region of the hilus and much blood in the peritoneal cavity. The patient recovered.

CASE 176 (Roettig, Nusbaum and Curtis, 1943).—A male college student was admitted to the hospital shortly after an automobile accident as a result of which he lost consciousness. He was not in shock. He remanied in the hospital, and on the eighth day sat up in a chair. The red cell count had fallen from 5,060,000 the day of admission to 3,420,000 the day he sat up. That evening he had sudden severe abdominal pain, with signs of shock. The red cell count was 2,600,000 and the white cell count 35,000. Operation performed after a blood transfusion revealed a ruptured subcapsular splenic hematoma, which was treated by tamponade and suture. Recovery ensued.

CASE 177 (Roettig, Nusbaum and Curtis, 1943).—An 18 year old boy entered the hospital with severe abdominal pain, nausea, vomiting and weakness of twelve hours' duration. Five weeks previously he had been struck in the left upper quadrant of the abdomen in an explosion. The temperature was now 100 F., the pulse rate 110, the respiratory rate 20 and the blood pressure 90 systolic and 50 diastolic. The

red cell count was 3,900,000 and the white cell count 22,400. The patient had severe pain with generalized abdominal rigidity and tenderness. At operation, a perisplenic hematoma was found with an associated laceration of the spleen. The laceration was sutured and the splenic fossa packed. The patient had an uneventful recovery.

ANALYSIS OF CASES

Age.—The greatest number of injuries occurs during the third decade of life, and the number remains relatively constant through the following three decades. This observation is at variance with the opinion of those who say that splenic injury is incurred most frequently in the younger age group. The youngest patient was 4 years old; the oldest, 61 years. In McIndoe's series most injuries occurred between the ages of 15 and 50 years.

Sex.—Fifty-five of the patients in this series were males; 15 were females, producing a ratio of 3.5 to 1. The ratio given in a previous large collection of cases was 9 to 1.

TABLE 3.—*Type of Accident Producing Delayed Splenic Rupture*

Falls	25
Automobile accidents	10
Assault and battery	8
Motorcycle accidents	8
Bicycle accidents	5
Run over by automobile	2
Blows by objects	6
Football injuries	2

Initial Injury.—The normal spleen is small and fixed in a protected position. Subcutaneous injuries to the spleen are usually the result of severe or moderately severe trauma. Robitshek was of the opinion that while slight trauma may produce these injuries, it is usually of a degree sufficient to produce other accompanying injuries. However, the damage to the spleen is of course slight, because temporary recovery usually takes place in a short time. Severe trauma, such as that due to a fall from a great distance, or to being pinned under a car, was responsible for 19 cases. Moderately severe trauma, such as is caused by an automobile accident, a fall or a blow by object or fist, accounted for 44 cases. In 5 instances the trauma was slight, being due to a fall while the patient was ice-skating or walking, to bumping the left side or to falling over a low fence. In only 1 case was the rupture spontaneous—the case of a man who felt a stitch in his side while lifting a heavy beam. This was probably the result of direct violence to the spleen by muscular compression. Injury directed to the left hypochondrium is markedly infrequent. It has also been noted that direct violence usually causes parenchymal and capsular lacerations, while indirect violence often is responsible for hilar tears. Table 3 presents the frequency of each type of injury.

Foster and Prey reported automobile accidents as the responsible factor in 70 per cent of 20 cases of immediate hemorrhage. Bailey (1927) found street accidents to be more important than falls (14 and 10 cases respectively out of a total of 32 cases of splenic rupture of all types), even though his report partially covered a period before the automobile (1894 to 1926). In another series of splenic ruptures of all types Connors reported that in 22 cases the trauma was caused by the patient's being struck by a vehicle and in 7 it was due to a fall. In 3 of Connors' cases there was a free interval of at least twenty-four hours. These occurred in a series of 32 subcutaneous ruptures of the spleen of all types, an incidence of 9 per cent. In the present series of cases of delayed hemorrhage automobile accidents were causative in 18 per cent, while falls accounted for 38 per cent. It appears that automobile accidents are more apt to produce immediate splenic hemorrhage, while falls are the most common cause of delayed rupture of the organ.

Latent Period.—The latent period, so termed by Baudet, a period of symptomatic relief following the injury, denotes the interval from the cessation of bleeding following the initial injury to the onset of secondary hemorrhage. The mechanisms of hemostasis involved will be discussed under pathogenesis. The duration varied from several hours to three months, but secondary hemorrhage occurred most often before the end of the first week. McIndoe stated that it took place most frequently from the third to the ninth day. Hageney (1939) found the interval in from 50 to 60 per cent of his cases to be less than one week, in 20 per cent from one to two weeks, and in the remainder less than thirty-nine days, with the exception of 1 patient who had an interval of six months. Orator (1939) presents a case of splenic rupture occurring two years after the patient was hit in the left side. The extremely long interval gives rise to doubt as to any connection between the original injury and the subsequent rupture. Schmid (1935) stated that no cases of delayed splenic rupture occurred with an interval of more than nineteen days. This is not strictly accurate, for in the present series there were 8 patients in whom bleeding began after twenty days. Furthermore, McIndoe's classic article cited 1 case with an interval of six months. Kallius (1942) stated that in 80 per cent of cases the capsule ruptures within the first week and in 20 per cent within the second or third week. Müller's third case (1940), with a two year latent period (case 171), seems to be quite authentic, however, the thick-walled, head-sized hemorrhagic cyst indicating the chronic course. Table 4 notes the frequency of the duration of the latent period.

It has been thought that a diagnosis of ruptured spleen could be made during the latent period and splenectomy performed before secondary

hemorrhage took place. Delannoy (1939) distinguished two clinical types of secondary hemorrhage: 1. Rupture with retarded symptoms, which corresponds with a perisplenic hematoma. With this type the patient continues to suffer pain in the left hypochondrium or shoulder. The temperature or pulse rate may be elevated. Gastrointestinal disorders occur. There may be persistent tenderness, rigidity or dulness. Roentgenograms may show a paralyzed diaphragm with a subjacent shadow. 2. Splenic ruptures with retarded hemorrhage, corresponding to intrasplenic or subcapsular hematoma. With this variety symptoms appear suddenly after a completely asymptomatic period.

Symptoms and Signs During Latent Period.—In the present series pain was the outstanding symptom during the latent period. It varied from abdominal discomfort to pain localized in the left upper quadrant, colicky or persistent. It was localized to the left upper quadrant in

TABLE 4.—*Length of the Latent Period Between Injury and Delayed Splenic Rupture*

Latent Period	Cases
5-48 hours	11
2- 6 days	22
7-11 days	15
12-16 days	7
21 days	1
23 days	1
27 days	1
28 days	1
35 days	1
41 days	1
3 months	1
2 years	1

only 4 instances. Two patients were unable to stand erect because this position initiated the pain. Rigidity and tenderness during the first few days after the accident were uncommon findings. In only 1 case was there definite enlargement of the abdomen. Systemic signs of bleeding, such as pallor, malaise, faintness, sweats and weakness were noted but were uncommon. One patient complained of pain on the left side of the lower part of the chest without a broken rib. One of our patients had an unexplained rise of temperature to 101 F. Definite evidence of a perisplenic hematoma during the latent period was not present in any case. McIndoe, however, was able to note a few instances of this variety of injury in which the following signs were present: fulness and an increase in splenic dulness, slight pallor, weakness, dizziness or occasional fainting. Costal breathing and an accelerated pulse rate were also reported. Quénu (1926) felt that a diagnosis of ruptured spleen could be made during latency on a person who after receiving trauma to the left hypochondrium presented a good general state but had some sensitivity in that area, a slight but persistent rigidity and a slight elevation in temperature. Oudard and Guichard (1932) stated

that two types of symptoms were present as a result of bleeding, with the accompanying peritoneal irritation: (1) pain in the splenic region with rigidity and increased splenic dulness, and (2) immobilization of the left lobe of the lung without pleural or pulmonary signs.

Pathologic Changes in Subcutaneous Rupture.—Obviously, the pathologic changes in this condition vary with the stages of the process, which are the initial injury, the latent period and the period of secondary hemorrhage.

Four types of initial injury are responsible for the progression of the symptoms. They are: (1) minor parenchymal contusions or capsular lacerations; (2) intrasplenic and subcapsular hematoma; (3) perisplenic hematoma with an initial parenchymal and capsular laceration; (4) tears of the pedicle.

The first type is purely theoretic, because the symptoms provoked are not severe. Minor injuries tend to form blood cysts or to heal spontaneously and do not warrant exploration. Undoubtedly the majority of intrasplenic and subcapsular hematomas remain as such, or they may continue to bleed, subsequently producing capsular ruptures and free peritoneal hematoma. The changes incident to a perisplenic hematoma will be discussed. It is rather difficult to see in what way hilar tears may be responsible for secondary hemorrhage. All of the authors whose cases are included in this report have cited instances of spontaneous rupture of a supposedly previously normal spleen. Zschau (1939) reported a delayed rupture of a leukemic spleen. Ruptures of malarial spleens are frequent, and Maes and Rives (1941) state that one thirtieth of all deaths in the malaria-infested area about Calcutta are due to such an accident.

In the present series, as in McIndoe's, intrasplenic bleeding occurred before rupture of the capsule in over 50 per cent of the cases. In a few cases there was an associated laceration of the capsule with a perisplenic hematoma. A combination of subcapsular hematoma and capsular laceration was present in only 14 of the 57 cases with available data. Lacerations were the most frequent operative finding. The violence of the secondary hemorrhage caused disruption of the spleen in 5 cases and detached the spleen in 1 case. Free or clotted blood in the peritoneal cavity was absent in only 1 case, an instance of subcapsular hematoma without a capsular tear. Table 5 summarizes the operative findings.

The pathogenesis of the latent period can be interpreted in various ways. This is an interesting field for speculation, and the following theories and observations have been offered:

1. Temporary hemostasis produced by the state of shock. Hemorrhage is concomitant with the injury. Should the hemorrhage from a splenic injury be severe enough to produce shock, temporary cessation

of bleeding is affected by the same processes as are seen in shock from other causes. This theory is more directly applicable to cases of immediate hemorrhage, in which it is frequently noted that improvement follows the initial shock stage.

2. Hematoma under tension. Intrasplenic bleeding may be made to cease by an enlarging hematoma which exerts compression on the contused pulp.

3. Theory of subcapsular hematoma. Demoulin expressed the belief that when bleeding is more or less abundant the capsule is detached and forms a sort of hood in which clots collect. Then from any cause whatever, even from distention, the capsule ruptures, producing intraperitoneal hemorrhage.

TABLE 5.—*Pathologic Changes in Delayed Splenic Rupture*

Changes in the Spleen	Cases
Tear of convexity	26
Tear of diaphragmatic surface	2
Tear of costal surface	1
Tear of superior pole	1
Tear of inferior pole	1
Multiple lacerations	3
Subcapsular hematoma	18
Multiple subcapsular hematoma	1
Complete decapsulation	1
Laminated perisplenic hematoma	1
Disruption of spleen	5
Spleen torn from pedicle	1
Torn pedicle	4
Tear through spleen into pedicle	1
Rupture of an infaret	1
No free blood in peritoneal cavity	1
Combined subcapsular or parenchymal hematoma and laceration of spleen or pedicle	14

4. Formation of clots at the laceration (Werthmann). Clots in various stages of organization have been observed rather frequently at the site of the laceration. The extrasplenic clot is detached readily even by minimal effort.

5. Tamponade by omentum (Mannheim, Routier, Nast-Kolb). Plugging of the laceration by omentum is believed to be one of the most effective means for arresting hemorrhage.

6. Tamponade by stomach, colon or adhesions (Oudard and Guichard). The distended stomach or colon may seal the laceration. Abnormal perisplenic adhesions may do the same. These organs help keep the clot in the laceration under tension.

7. Theory of perisplenic hematoma (Delannoy, McIndoe). The spleen is surrounded by a potential space bounded on all sides by organs which are easily displaced. Hemorrhage from the injury surrounds the spleen, elevates the diaphragm and displaces the splenic flexure of

the colon and the parietal walls. Adhesions are formed, uniting the various organs and producing an enclosure which does not permit peritoneal flooding.

8. Theory of threshold of hemorrhage (Laporte). The organism can tolerate some hemorrhage, but at a certain threshold signs of hemorrhage appear. This theory is borne out by those cases that have an onset prolonged over several hours.

Kment in 1930 reviewed 42 cases of delayed rupture and found that in 8 of these there was self tamponade with blood clots and in 3 with adhesions. In Herfarth's series there were 8 cases of tamponade by clots, 1 of tamponade by omentum and 2 of tamponade by adhesions. Hageney (1939) collected 70 cases of delayed splenic rupture, in 75 per cent of which the condition was due to rupture of a subcapsular hematoma and in the remainder to temporary blockage of the tear with clots, omentum or other organs.

Secondary Hemorrhage.—The symptoms and signs of splenic hemorrhage are those of peritoneal and diaphragmatic irritation, shock and hemorrhage. It is a matter of no small surprise to have an onset of severe pain or shock following minor exertion or apparently coming on spontaneously. In 4 cases the onset occurred while the patient was straining at stool. In 1 patient it occurred when he was arising from bed, and in another, while she was washing clothes. Frequently it occurred when no unusual stress was present.

The usual abrupt onset of secondary hemorrhage initiates a characteristic train of symptoms. It is ushered in with pain in the abdomen, chest or shoulder. The abdominal pain, varying in severity, may be general or localized to the left side of the abdomen, left hypochondrium, epigastrium, upper part of the abdomen or periumbilical region. In only 1 patient was abdominal pain absent. Pain in the left shoulder (Kehr's sign) was present in 19 of 68 recorded cases, and pain low in the left side of the chest was the presenting symptom in 3 cases. Kroh (1939) doubted the importance of pain in the left shoulder as a sign of splenic rupture. In a series of 7 cases of splenic trauma personally observed during the previous three years, this author did not once see a positive example of this sign. Tenderness was generalized or localized to the left upper quadrant of the abdomen. In only 1 instance (Dodd's first case, our case 137) was it over the cecum, and this patient was the only one who had diarrhea. Dodd's explanation of this phenomenon is as follows: Bleeding from the lacerated spleen irritates the splenic flexure and descending colon into contraction, thus causing the diarrhea. Later, this segment of bowel becomes paralyzed by aseptic peritonitis. The ensuing partial intestinal obstruction is followed by distention and tenderness of the cecum in the right iliac fossa. Nyström (1918) reported 3 cases of immediate splenic rupture

in which intestinal distention was severe. Rigidity, when present, was more often general than local. In 3 cases with pain, rigidity and tenderness were absent. McIndoe expressed the opinion that rigidity in abdominal contusions, not limited to the injured part, is of diagnostic significance and is a clear indication for laparotomy.

Nausea or vomiting occurred in 17 cases. Diarrhea and constipation were each present once.

Collapse, or shock resulting from hemorrhage, soon follows or may be an initial sign. Shock was noted in 31 instances and syncope in 4. The accompanying signs of hemorrhage were noted as follows: Low blood pressure was recorded in only 8 cases; in 3 it was normal at the onset. Acute anemia was recorded 18 times. Pallor was present in 28 cases. Weakness, sweating, restlessness and air hunger also were noted. Fifteen patients had a white cell count ranging from 12,000 to 43,000. In 1 case there was a normal white cell count. The symptoms of shock and hemorrhage are indistinguishable clinically, except in those patients who improve after the initial shock but have symptoms of hemorrhage later. Furthermore, the two conditions need not be differentiated, since they are treated in a similar manner (Harkins). Berger stated that 51.8 per cent of patients with a ruptured spleen die within one hour as the result of hemorrhage. Seven of McIndoe's patients died before anything could be done for them.

The presence of blood in the peritoneal cavity may be determined by percussion. Dulness limited to the splenic region or in the left flank was noted in 23 cases. A fluid wave was obtained in 7 instances. Ballance's sign, fixed dulness in the left flank due to the enlarging hematoma and shifting dulness in the right flank, was present in 1 case. This sign should be present at some time during the course of the disease. Abdominal distention was observed 9 times.

The temperature was most frequently normal or subnormal. Slight elevations are not uncommon, but temperatures above 100 F. are distinctly rare. The pulse is usually rapid and poor in quality. In 10 instances the pulse rate was below 90. Respiration is rapid and costal in type.

Two signs are frequently cited in the literature:

Ballance's sign, shifting dulness in the right flank and fixed dulness in the left, indicates a large amount of free blood as well as a large hematoma. Bailey (1927) stated that there are many references to this sign in the literature but that the consensus seems to be that it is so rarely present as to be almost valueless. Connors (1928) noted it in only 1 of 32 subcutaneous splenic ruptures. Rousselot and Illyne noted it in 5 of 17 cases. In our series it was also noted only once.

Kehr's sign is referred pain in the left shoulder due to stimulation of the phrenic nerve. Bailey (1927) found this sign quite evident

in certain of his cases of ruptured spleen. Rousselot and Illyne noted it in 4 of 17 cases. Kehr's sign was present in at least 28 per cent of our cases and was a much more useful diagnostic help than Ballance's sign.

Diagnostic Aids.—Leukocytosis and the anemia of hemorrhage have already been discussed. Roentgen examination has proved of value in establishing a diagnosis in a few cases. Webb (1939) reported the following changes in a typical case: (1) increased density in the left upper quadrant of the abdomen; (2) elevation of the left side of the diaphragm; (3) displacement of the stomach to the right side; (4) free fluid between loops of the intestine. In 1 of our cases with continuing hemorrhage the diaphragm was markedly elevated. In another case we observed recently the colon was displaced medially and a shadow marking a mass was present in the left upper quadrant of the abdomen. Bancroft (1942) noted a separation of the air shadow in the stomach when the patient was in an inverted position. Bancroft's patient, a boy aged 11 years, was in the hospital for three days after receiving a blow to the left side. The temperature was 100 F.; the hemoglobin content of the blood was 70 per cent, and the patient felt quite weak. Bancroft gave the patient barium sulfate by mouth, put him in the Trendelenburg position and observed a mass in the region of the spleen displacing the stomach. Operation revealed a lacerated spleen with a massive hematoma. Splenectomy was performed. This is one of the few cases in which operation was done to forestall a secondary rupture of the spleen. Burke and Madigan (1933) administered colloidal thorium dioxide (24 cc.) to a patient with a ruptured liver and spleen after operation, and were able to outline the ruptures in these organs. One half of the usual dose is used. They thought this procedure might be of value when physical signs are obscured, as by alcoholism. However, this procedure requires about four hours and is not without danger.

Paracentesis has been recommended by Wright and Prigot. In 13 out of 15 cases, including 2 cases of delayed hemorrhage, the result of the test proved positive, i. e., blood was obtained. Two "false positive" results were obtained on patients with ruptured kidneys. The tap may have to be repeated if the patient continues to show signs of internal bleeding and the first tap gives a negative result. Vaginal puncture has been used to obtain peritoneal blood. Bumm (1931) used this procedure on a patient with a preoperative diagnosis of ruptured ectopic pregnancy.

Peritoneoscopic examination has not been used, but it may be of value in doubtful cases.

Associated Lesions.—Other lesions resulting from the initial injury may obscure the underlying splenic trauma. Fractured ribs on the left side were noted in 11 instances. McIndoe noted this feature in

10 of his 46 cases. Intrathoracic hemorrhage and pneumothorax on the left side were seen once. Contusion and laceration of the kidney and a hematoma of the mesentery were also present. Fractures of other bones were rare and are unimportant from a diagnostic standpoint. De Monie found fractured ribs in 10 per cent of his cases, while lesions of the left kidney accounted for 12 per cent. In 5 per cent there was accompanying damage to the lungs. This frequency of fractured ribs with splenic rupture should make one suspicious of the underlying splenic injury.

Preoperative Diagnosis.—A correct diagnosis of splenic bleeding was made in 20 cases. Internal hemorrhage was diagnosed in an additional 12 cases. The following mistaken diagnoses were made: ruptured ectopic pregnancy in 3 cases; perforated peptic ulcer, peritonitis and acute appendicitis, twice each; acute pancreatitis and pneumonia, once each. In 24 cases a preoperative diagnosis was not presented.

Results of Operation.—Difficulty in diagnosis and watchful waiting are the causes for the high mortality. Kallius (1942) points out that the prognosis of secondary rupture of the spleen is less favorable than that of primary rupture. The patient remembers that the first abdominal crisis soon passed off and believes that the new attack will do likewise. Thus time is lost, and he does not seek medical help sufficiently soon. Although all of the symptoms of primary splenic hemorrhage (increased splenic dulness and progressive anemia, local tenderness, pain in the left shoulder, retraction of the testicle on the left side, vagus pulse, increasing pain when the patient lies on the back, and shock going on to collapse) may not be present, at least some of them are usually evident, and the patient is usually clear as to the determining injury. Kallius believes that in this last regard a history of evanescent shock associated with hyperesthesia of the left phrenic nerve is especially significant. It has been stated that in ordinary splenic rupture the average interval between admission and the time of operation is twelve hours. Those who continue to keep patients with ruptured spleens under observation for a protracted period fail to realize the seriousness of this surgical emergency. We believe that all patients with ruptured spleen for whom a diagnosis can be made during the latent period should have the benefit of immediate surgical treatment. Whenever a definite diagnosis cannot be made but the suspicion of a splenic rupture is entertained, it is best to keep the patient at rest in bed for at least two weeks to lessen the possibility of delayed hemorrhage. During this time enemas are forbidden. Food is not withheld. Blood counts should be made several times daily, and progress roentgenograms of the abdomen should be taken at intervals.

In 62 cases in which the result was mentioned, 53 patients recovered and 9 died, a gross mortality of 14.5 per cent. Fifty-seven patients had

undergone splenectomy; 3 had tamponade and in 4 the spleen was not removed. Six patients died after splenectomy, a mortality of 10.5 per cent.

McIndoe reported an operative mortality of 27 per cent. Seven patients died before anything could be done. Of 9 patients that were not operated on, 8 died.

In untreated splenic rupture the mortality ranges from 77 to 100 per cent. Berger reported a 93 per cent fatality rate in 220 cases of splenic rupture of all types in which no operation was done. The mortality rate reported by Watkins was 100 per cent, by Connors 100 per cent and by Lemerenz 77 per cent. Zschau (1939), in a report on a probable case, stated that the patient bled secondarily on the fifth day but recovered with conservative management.

Regarding the type of operation, splenectomy is the only procedure to be used. Tamponade is uncertain, and bleeding may not be controlled. Splenorrhaphy carries a mortality of 5 to 20 per cent. Dretzka, reporting a preponderance of gunshot and stab wounds, was enthusiastic about repair and tamponade, and he had a mortality of 20 per cent among 10 patients. Tamponade has only a single indication—the patient who is a very poor risk and for whom splenectomy would be fatal. Splenectomy, however, offers the quickest means of stopping hemorrhage and with modern methods of prophylaxis and treatment of shock with plasma and serum has extended indications.

The technic of splenectomy has been admirably covered recently by Cole, and a new technic has been described by Rives for splenectomy in the presence of difficult adhesions. Several special features, however, are worthy of mention. Bailey (1923) stated that the pedicle is found to be friable only in cases of delayed hemorrhage. His explanation of this point is that the pedicle after being surrounded by mildly irritating blood itself becomes edematous and undergoes degeneration. It is far safer to employ individual ligatures applied by transfixion close to the spleen than a mass ligature, which is more likely to cut. Michels (1942) pointed out the fact that the position of the splenic artery is as variable as that of the cystic artery. When preliminary ligation or clamping of the artery is done it is occasionally difficult to find the vessel, because its position may be prepancreatic, intrapancreatic, retropancreatic or suprapancreatic. The main splenic artery divides into its two terminal branches from 1 to 7 cm. from the hilus, and in most instances there are two hili.

Complications.—Dehiscence of the abdominal wound has been seen frequently. Bailey reported that in 4 of 32 cases in which the paramedian incision was used the wound burst open. Connors noted 3 cases of severe suppuration of the abdominal wall following splenectomy for rupture. The cause for what is called suppuration is undoubtedly

digestion of the edges of the wound by pancreatic enzymes which result from injury to the pancreas. This may also be a factor in disruption. Studies of vitamin C, plasma protein and diastatic activity were not done on any of the patients with disruption. Injury to the pancreas, of course, does not always cause digestion of the abdominal wall or separation of the edges of the wound. In 1 of the patients in the present series damage to the tail of the pancreas was not followed by any complication. In the present series the following complications occurred: 2 wound disruptions, 1 severe wound infection, 2 cases of intestinal obstruction, and 1 each of pleural effusion and pneumonia. There were also 2 cases of phlebitis and 1 of anuria from a transfusion reaction.

Late Results.—The late results of splenectomy are chiefly anemia and leukocytosis which persist for months. Lymphoid hypertrophy may occur (Pfeiffer and Smyth), and a persistent enlargement of the superficial glands may be noted.

SUMMARY AND CONCLUSIONS

All of the available reports concerning delayed splenic rupture have been collected. The total of 177 cases, while it represents over two and one-half times as many instances of this syndrome as have been reported in any previous summary, still does not represent the true frequency of this condition. Traumatic rupture of the normal spleen is the most common serious subcutaneous abdominal injury. Delayed splenic rupture (the *hémorragie en deux temps* of the French, or *zweizeitige Milzruptur* of the Germans) represents about 14 per cent (1 in 7) of all splenic ruptures. This syndrome is especially insidious and treacherous because of the almost symptom-free latent period, but the delay offers an opportunity for diagnosis and treatment.

Delayed splenic rupture is most common in males in the third decade of life. Falls and traffic accidents are the most common etiologic agents. About 50 per cent of the secondary ruptures occur after an interval of less than seven days, while in an additional 25 per cent the latent period ends during the second week. Fractured ribs on the left side occur in about 10 per cent of the cases, while Kehr's sign (pain in the left shoulder due to irritation of the phrenic nerve) is present in about 28 per cent or more of cases. Other diagnostic aids include those used in diagnosing any type of splenic rupture, such as sudden collapse or shock, rapid or increasing pulse rate, progressive anemia, white cell count from 12,000 to 20,000, absence of temperature over 99 F., pain, tenderness, dulness and rigidity in the left upper quadrant, and in some instances signs of free fluid in the peritoneal cavity.

Without operation the mortality ranges from 77 to 100 per cent. At the time of McIndoe's review (1932) the operative mortality was

27 per cent. but during the past decade it has been only 10 per cent. When splenic laceration is suspected the patient should be kept in bed under close observation. In more definite cases, or at the first sign of secondary hemorrhage, splenectomy should be performed. Adequate treatment of shock with plasma or whole blood forms a necessary adjunct to the operative procedure.

ADDENDUM.—Since this paper was written a review on the subject has been published by W. H. Bueermann. In this article 2 additional cases are reported. In the first, that of a man aged 22 years, the rupture occurred thirty-eight days after he hit the left side of his chest and abdomen against a steering mechanism when his ship was torpedoed. The second is the case of a seaman aged 17 years, whose spleen ruptured four days after a fall on a dock. Addition of Bueermann's 2 cases brings the total of reported instances of delayed splenic rupture to 179.

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INORGANIC PHOSPHORUS CONTENT OF THE SERUM IN SHOCK

GEORGE W. DUNCAN, M.D.*
BALTIMORE

In a recent study of experimental crush injuries great elevation of creatine in the blood and the urine was observed.[1] This elevation was believed to arise chiefly from injury to skeletal muscle. Since at least a large part of the creatine in muscle exists in combination with phosphoric acid, it seemed likely that inorganic phosphate would also be liberated. Accordingly, the levels of serum inorganic phosphorus were determined for several animals subjected to these injuries and were found to be strikingly high. A more detailed study, including shock produced by other methods, was then undertaken.

EXPERIMENTAL METHOD

Dogs were used in all experiments. Anesthesia was produced by the subcutaneous injection of 0.030 Gm. of morphine sulfate followed thirty minutes later by the intravenous injection of soluble pentobarbital U. S. P. (pentobarbital sodium) in doses of 0.02 Gm. per kilogram of body weight. Subsequent injections of 0.006 Gm. per kilogram were occasionally necessary. Arterial pressures were determined by direct puncture of the femoral artery. Hematocrit readings were made with Wintrobe tubes. Serum inorganic phosphorus levels were determined by the method of Fiske and Subarrow.[2] Immediately after withdrawal of blood samples from animals subjected to trauma by hammer blows or crush injury, an equal amount of blood from another animal was injected in order to exclude the effect of hemorrhage. Shock was produced by crush injury of an extremity, by hammer blows to an extremity and by hemorrhage.

The method and other details of the experiments on crush injury have been reported elsewhere.[1] For 12 of the animals subjected to these injuries, serum inorganic phosphorus levels were determined at the beginning of the experiment, at one hour, two hours, three hours, four hours, four and a half hours, five hours, five and a quarter hours, five and a half hours, six hours, seven to eight hours, and nine to eleven hours. In the experiments in which shock was produced by

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* William Stewart Halsted Fellow in Surgery.

From the Department of Surgery, Johns Hopkins University School of Medicine, and Johns Hopkins Hospital.

1. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, Ann. Surg. **115**:684, 1942.

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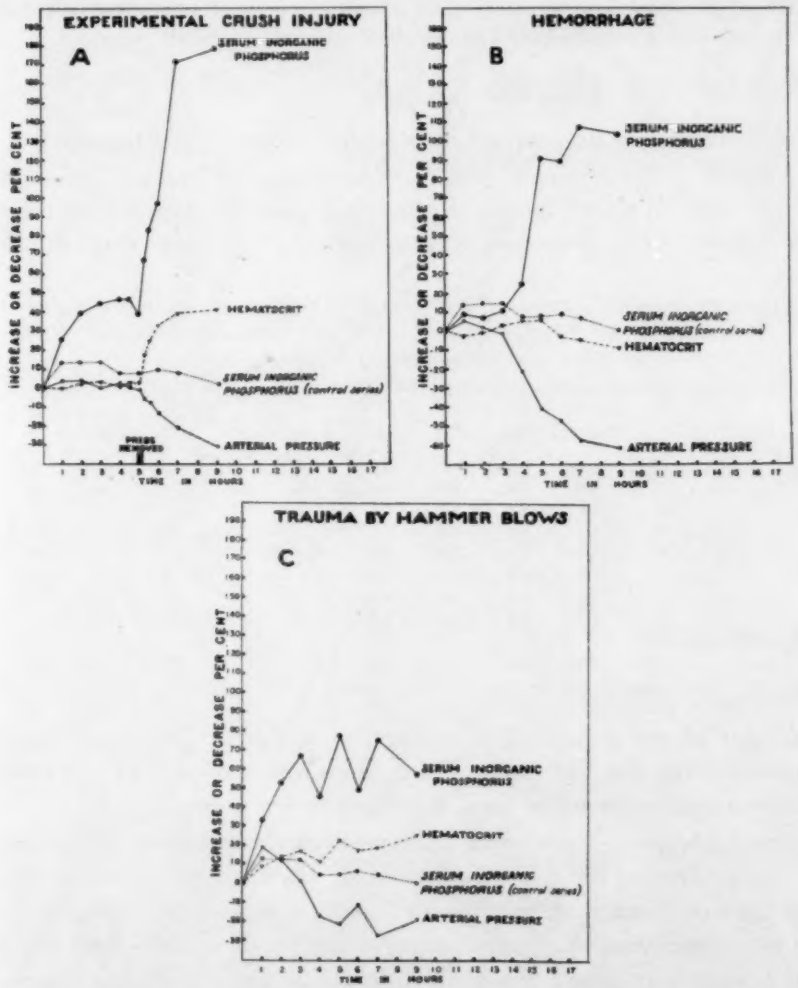
hammer blows, repeated blows as nearly uniform as possible were administered to the soft tissues of a hindlimb, care being taken to avoid the large vessels and nerves. Shock due to hemorrhage was produced by withdrawal of blood from the femoral vein in amounts equaling 0.5 per cent of body weight at thirty minute intervals until the arterial pressure fell to approximately 70 mm. of mercury.



Changes observed in serum inorganic phosphorus, arterial pressure and hematocrit reading in shock produced by experimental crush injury, trauma by hammer blows and hemorrhage. The values expressed in percentages are computed from the averages of the experiments in each group.

In some animals subsequent bleeding was necessary to maintain the pressure at this level. In the case of hemorrhage and of trauma produced by hammer blows, serum inorganic phosphorus levels were determined hourly for the first six hours.

Subsequent observations were made at seven to eight hours and again at nine to eleven hours. In all three groups of experiments the hematocrit reading and the arterial pressure were observed at the same intervals at which the serum inorganic phosphorus level was determined.

Several control experiments were performed in order to determine the effects of anesthesia on the level of serum inorganic phosphorus. The animals were restrained on tables as in the other types of experiments and were given morphine sulfate and soluble pentobarbital (pentobarbital sodium) as already described.

RESULTS

The results are summarized in tables 1, 2, 3 and 4 and the chart.

Control.—There were 8 control experiments. Elevation above the control levels of serum inorganic phosphate was observed in 6 of the 8 experiments. The elevation was greater in 1 animal than in the

TABLE 1.—*Serum Inorganic Phosphorus (Milligrams per Hundred Cubic Centimeters) as Affected by Anesthesia and Restraining Animal on Table for Several Hours (Control Series)*

Dog	Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	7 to 9 Hr.	9 to 12 Hr.
1	4.0	4.2	4.7	4.6	4.2	4.3	4.5	4.3	4.3
2	4.6	4.8	4.1	4.3	4.4	4.6	4.6	4.6	4.6
3	4.2	8.3	9.1	9.9	7.1	7.1	6.9	6.6	3.1
4	7.3	8.3	8.3	7.7	7.1	7.0	6.8	5.8	6.8
5	7.4	8.3	7.6	7.3	7.0	7.1	7.7	7.1	8.1
6	7.9	7.2	5.8	5.2	4.4	5.0	4.4	5.9	6.2
7	3.6	2.7	3.0	3.6	3.6	4.3	4.6	4.5	4.0
8	4.1	4.9	5.9	5.9	7.6	6.2	6.8	7.0	6.5
Average increase or decrease	5.4	6.1	6.1	6.1	5.7	5.7	5.8	5.7	5.5

remainder of the group. The average of the group showed a slight increase during the first three hours, after which there was a decline to approximately the initial level at nine to twelve hours.

Crush Injury.—There were 12 experiments in which crush injury was used. During the five hour period in which the press was on the thigh no significant change in arterial pressure was noted. No significant hemoconcentration occurred, the average for the entire group being only 1.2 per cent above the control values at the end of five hours. During the same period an increase in the level of serum inorganic phosphorus occurred, and although the increase was slight in some animals, the average rise was greater and more sustained than that observed in the group of animals subjected to anesthesia alone.

On removal of the mechanical press at the end of five hours, rapid changes in all the criteria under observation became evident. Within fifteen minutes after removal of the press the hematocrit reading showed

TABLE 2.—*Serum Inorganic Phosphorus Changes (Milligrams per Hundred Cubic Centimeters) Following Experimental Crush Injury*

Dog	Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	5 Hr. 15 Min.	5 Hr. 30 Min.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1 Serum inorganic phosphorus (mg.												

TABLE 2.—*Serum Inorganic Phosphorus Changes (Milligrams per Hundred Cubic Centimeters) Following Experimental Crush Injury*

Dog		Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	4 Hr. 30 Min.	5 Hr.	5 Hr. 15 Min.	5 Hr. 30 Min.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1	Serum inorganic phosphorus (mg. per 100 cc.)	2.7	3.6	4.5	4.5	4.6	5.5	4.6	6.7	6.2	7.9	11.7	18.0	No therapy; died 12 hr. after press was removed
	Hematocrit reading	56.0	55.3	54.8	54.6	54.8	58.3	56.8	60.6	62.3	66.4	69.8	70.4	
	Arterial pressure (mm. of mercury)	130	120	130	130	120	130	120	115	120	105	85	75	
2	Serum inorganic phosphorus (mg. per 100 cc.)	5.2	7.2	6.3	7.3	8.0	7.8	5.3	6.3	7.8	8.4	7.6	7.7	No therapy; died 9 hr. after press was removed
	Hematocrit reading	51.3	53.9	54.2	50.3	48.2	47.7	47.8	56.8	66.8	68.0	68.8	67.0	
	Arterial pressure (mm. of mercury)	125	135	135	130	135	130	130	125	110	95	75	45	
3	Serum inorganic phosphorus (mg. per 100 cc.)	3.4	4.8	4.9	6.3	4.9	5.0	5.3	5.3	6.8	7.6	11.2	9.7	No therapy; died 9 hr. after press was removed
	Hematocrit reading	42.9	41.7	46.6	44.8	46.3	46.8	49.6	57.3	59.6	66.7	68.4	70.2	
	Arterial pressure (mm. of mercury)	125	135	130	125	130	130	125	120	120	105	110	50	
4	Serum inorganic phosphorus (mg. per 100 cc.)	5.5	5.6	7.2	6.7	7.0	7.2	7.4	8.2	9.1	9.6	10.1	11.7	No therapy; died 12 hr. after press was removed
	Hematocrit reading	44.3	45.4	47.7	51.2	48.4	48.2	49.3	53.4	56.9	58.6	62.8	64.7	
	Arterial pressure (mm. of mercury)	125	125	120	120	115	115	120	115	115	95	90	70	
5	Serum inorganic phosphorus (mg. per 100 cc.)	4.8	4.9	5.9	6.4	7.1	6.4	5.9	6.4	6.7	8.2	17.7	....	No therapy; died 2 hr. 15 min. after press was removed
	Hematocrit reading	42.2	46.2	46.8	48.3	44.8	43.0	42.3	54.3	55.4	67.7	72.7	....	
	Arterial pressure (mm. of mercury)	130	130	125	125	130	125	125	105	95	85	50	....	
6	Serum inorganic phosphorus (mg. per 100 cc.)	4.4	5.4	5.4	4.5	4.8	4.8	4.8	7.5	7.1	8.5	12.5	9.6	No therapy; died 5 hr. 15 min. after press was removed
	Hematocrit reading	53.2	49.0	49.4	51.3	48.4	49.7	48.9	65.4	70.6	75.8	77.0	78.0	
	Arterial pressure (mm. of mercury)	130	135	130	130	135	130	130	125	115	100	90	60	
7	Serum inorganic phosphorus (mg. per 100 cc.)	3.7	4.4	4.9	6.7	5.4	5.3	5.0	5.4	6.3	7.0	9.1	8.7	Pneumatic cuff applied for 18 hr.; died 25 hr. after press was removed
	Hematocrit reading	55.8	51.6	51.8	50.3	50.3	51.5	51.3	62.3	65.8	70.0	76.3	76.3	
	Arterial pressure (mm. of mercury)	120	130	130	130	130	130	130	125	130	130	115	110	
8	Serum inorganic phosphorus (mg. per 100 cc.)	4.2	6.8	5.8	5.9	6.2	8.4	8.2	10.6	10.0	9.1	12.2	13.3	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading	47.7	50.0	50.0	47.7	47.0	47.2	47.7	53.2	54.2	57.8	63.2	63.0	
	Arterial pressure (mm. of mercury)	130	140	140	135	130	135	135	125	125	130	130	130	
9	Serum inorganic phosphorus (mg. per 100 cc.)	4.6	4.8	5.4	5.9	5.4	5.4	5.5	6.9	7.0	7.6	11.9	16.4	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading	55.2	56.7	57.7	59.1	61.0	61.3	63.0	63.9	65.4	65.2	65.4	66.7	
	Arterial pressure (mm. of mercury)	135	130	130	120	125	120	115	110	110	100	100	95	
10	Serum inorganic phosphorus (mg. per 100 cc.)	3.4	4.9	7.8	5.5	7.1	5.8	5.1	7.0	7.7	8.8	11.4	9.6	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading	50.0	50.2	51.7	51.3	52.8	51.4	51.6	56.0	59.8	63.2	67.0	66.4	
	Arterial pressure (mm. of mercury)	130	135	135	130	140	140	140	130	125	130	125	120	
11	Serum inorganic phosphorus (mg. per 100 cc.)	4.2	4.8	6.0	6.9	6.2	5.8	6.8	7.7	7.6	7.1	11.5	7.3	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading	43.7	43.3	45.7	41.5	45.4	44.2	46.8	49.7	52.0	55.6	58.0	60.3	
	Arterial pressure (mm. of mercury)	130	140	135	125	125	120	120	120	120	120	115	115	
12	Serum inorganic phosphorus (mg. per 100 cc.)	5.7	7.4	7.7	8.1	8.4	7.8	7.8	8.0	11.9	12.6	13.5	20.8	Pneumatic cuff applied for 18 hr.; died 16 hr. after press was removed
	Hematocrit reading	50.2	47.3	47.7	51.4	47.4	48.0	47.6	61.0	66.4	72.2	74.8	80.4	
	Arterial pressure (mm. of mercury)	125	130	130	125	125	125	125	115	120	125	125	100	
Average increase or decrease														
	Serum inorganic phosphorus (mg. per 100 cc.)	4.3	5.4	6.0	6.2	6.3	6.3	6.0	7.2	7.9	8.5	11.7	12.0	
	Hematocrit reading	49.4	49.2	50.3	50.2	49.6	49.8	50.2	57.8	61.3	65.6	68.7	69.4	
	Arterial pressure (mm. of mercury)	127.1	132.1	130.8	127.1	128.8	127.5	125.4	119.2	117.0	110.0	100.8	88.2	

a distinct increase and arterial pressure had begun to decline. The hematocrit reading at nine to eleven hours averaged 69.4, while the control average was 49.4. Arterial pressure had declined from the control value of 127.1 mm. of mercury to 88.2 mm. Serum inorganic phosphorus showed a sharper more progressive rise from its five hour level, averaging 12.0 mg. per hundred cubic centimeters at nine to eleven hours. This represented a rise of 179 per cent over the average control value of 4.3 mg. per hundred cubic centimeters. Six of these animals were treated by application of pressure to the injured extremity with a pneumatic cuff,[1] but distinct alterations in the criteria under observation occurred in spite of this form of therapy. Eight of the 12 animals died in an average time of eleven and three-tenths hours following removal of the mechanical press.

Hemorrhage.—There were 8 experiments in which hemorrhage was employed. The average duration of life was eight and seven-tenths hours. A decline in arterial pressure was observed in an average of four hours after bleeding was begun. The changes in hematocrit readings were not great; a slight average rise was noted four to five hours after bleeding was begun. This rise was followed by a decline in those animals which survived for longer periods. Distinct changes in serum inorganic phosphorus were observed, but in these experiments the early rise in inorganic phosphate was less pronounced than it was in the experimental crush injuries or with trauma produced by hammer blows. Elevation of inorganic phosphate was observed before the arterial pressure fell in 5 experiments, at the time of fall in arterial pressure in 1 experiment and following the fall in arterial pressure in 2 experiments. The average early values of this group more nearly conform to the early average values of the control series than do those of either of the other groups. Blood drawn at the time of death from the hearts of 3 of these animals and from the femoral vein of another showed an average of 22.5 mg. per hundred cubic centimeters.

Trauma by Hammer Blows.—There were 5 experiments in which trauma by hammer blows was used. Four of the 5 animals died in an average time of seven and nine-tenths hours following trauma. Progressive hemoconcentration occurred in the animals in these experiments but was not so great as in the animals subjected to crush injury. Arterial pressure declined in all experiments. Distinct elevation of serum inorganic phosphorus was observed. Two of the animals were more refractory to trauma than the others of the group; additional trauma to 1 of these at the end of six hours resulted in profound shock and death. It is to be noted that the inorganic phosphorus levels in these 2 animals

TABLE 3.—*Serum Inorganic Phosphorus (Milligrams per Hundred Cubic Centimeters) Following Hemorrhage*

Dog		Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1	Serum inorganic phosphorus (mg. per 100 cc.)	6.6	6.6	7.8	7.7	7.8	8.0	9.9	14.0	....	Died 8 hr. after hemorrhage was begun
	Hematocrit reading	55.7	50.0	50.9	52.2	55.0	56.2	52.0	52.1	....	
	Arterial pressure (mm. of mercury)	120	115	110	100	95	70	40	20	....	
2	Serum inorganic phosphorus (mg. per 100 cc.)	6.2	6.9	7.1	8.5	10.4	12.1	16.3	16.9	18.3	Died 10 hr. after hemorrhage was begun
	Hematocrit reading	46.3	44.7	45.5	45.5	42.2	39.8	36.6	36.6	37.6	
	Arterial pressure (mm. of mercury)	130	138	142	128	128	108	68	46	42	
3	Serum inorganic phosphorus (mg. per 100 cc.)	5.2	6.0	6.3	4.9	5.1	7.7	9.2	8.9	7.2	Died approximately 16 hr. after hemorrhage was begun
	Hematocrit reading	51.2	54.3	49.5	56.3	59.0	55.3	54.0	51.9	51.0	
	Arterial pressure (mm. of mercury)	130	132	110	108	86	66	65	68	68	
4	Serum inorganic phosphorus (mg. per 100 cc.)	3.8	5.2	5.4	4.2	4.2	8.8	9.8	10.4	12.2	Died 9 hr. 35 min. after hemorrhage was begun
	Hematocrit reading	41.0	38.0	39.4	45.0	48.3	43.7	42.8	41.7	41.0	
	Arterial pressure (mm. of mercury)	102	110	102	104	110	65	70	60	50	
5	Serum inorganic phosphorus (mg. per 100 cc.)	4.6	5.2	3.1	6.2	6.5	11.3	....	....	....	Died 5 hr. 50 min. after hemorrhage was begun
	Hematocrit reading	51.2	50.2	53.7	59.2	64.2	58.4	....	....	....	
	Arterial pressure (mm. of mercury)	124	142	140	138	134	78	....	....	....	
6	Serum inorganic phosphorus (mg. per 100 cc.)	7.9	8.5	7.8	7.2	9.1	20.1	....	....	....	Died 5 hr. after hemorrhage was begun
	Hematocrit reading	39.8	37.0	37.8	39.2	35.3	....	....	....	....	
	Arterial pressure (mm. of mercury)	100	104	104	110	62	....	....	....	....	
7	Serum inorganic phosphorus (mg. per 100 cc.)	6.7	6.0	5.7	5.1	6.3	8.2	9.0	8.6	8.6	Died 6 hr. 5 min. after hemorrhage was begun
	Hematocrit reading	45.6	43.4	43.0	44.0	44.2	44.8	45.0	45.4	43.8	
	Arterial pressure (mm. of mercury)	108	118	122	118	66	70	60	58	30	
8	Serum inorganic phosphorus (mg. per 100 cc.)	4.9	5.1	5.8	6.2	7.6	10.9	....	....	....	Died 5 hr. 40 min. after hemorrhage was begun
	Hematocrit reading	50.1	51.3	50.0	53.4	54.2	53.6	....	....	....	
	Arterial pressure (mm. of mercury)	116	126	126	108	46	24	....	....	....	
Average increase or decrease											
	Serum inorganic phosphorus (mg. per 100 cc.)	5.7	6.2	6.1	6.3	7.1	10.9	10.8	11.8	11.6	
	Hematocrit reading	47.6	46.1	46.2	49.4	50.3	50.3	46.1	45.5	43.4	
	Arterial pressure (mm. of mercury)	116.3	123.1	119.5	114.2	90.9	68.7	60.6	50.4	47.5	

TABLE 4.—*Serum Inorganic Phosphorus (Milligrams per Hundred Cubic Centimeters) Following Trauma by Hammer Blows to Extremity*

Dog		Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1	Serum inorganic phosphorus (mg. per 100 cc.)	5.2	12.2	15.1	18.0	....	....	....	....	....	Died 3 hr. 20 min. after trauma
	Hematocrit reading	41.8	47.0	49.1	50.2	....	....	....	....	....	
	Arterial pressure (mm. of mercury)	124	136	138	98	....	....	....	....	....	
2	Serum inorganic phosphorus (mg. per 100 cc.)	4.6	6.2	6.9	7.0	7.2	6.4	5.2	6.8	8.2	Recovered
	Hematocrit reading	54.9	56.2	59.0	61.7	....	60.1	58.2	57.0	58.2	
	Arterial pressure (mm. of mercury)	108	122	112	116	96	98	100	94	94	
3	Serum inorganic phosphorus (mg. per 100 cc.)	7.6	8.0	9.9	11.8	11.8	20.1	....	....	....	Died 5 hr. 10 min. after trauma
	Hematocrit reading	45.0	49.7	53.4	55.7	56.8	58.5	....	....	....	
	Arterial pressure (mm. of mercury)	114	148	136	114	60	30	....	....	....	
4	Serum inorganic phosphorus (mg. per 100 cc.)	6.9	6.7	6.8	4.9	6.0	7.0	9.7	11.4	11.6	Died 14 hr. after initial trauma; additional trauma to thigh at end of 6 hr.
	Hematocrit reading	36.8	45.3	47.3	47.3	49.2	52.0	51.2	49.1	53.0	
	Arterial pressure (mm. of mercury)	108	146	140	138	120	130	130	90	88	
5	Serum inorganic phosphorus (mg. per 100 cc.)	7.2	8.8	9.2	10.8	11.8	11.4	13.4	15.8	....	Died 9 hr. after trauma
	Hematocrit reading	43.4	42.0	43.7	44.1	42.0	46.8	47.4	52.0	....	
	Arterial pressure (mm. of mercury)	105	110	108	102	92	94	70	58	....	
Average increase or decrease											
	Serum inorganic phosphorus (mg. per 100 cc.)	6.3	8.4	9.6	10.5	9.2	11.2	9.4	11.3	9.9	
	Hematocrit reading	44.4	48.0	50.5	51.8	49.3	54.3	52.3	52.7	55.6	
	Arterial pressure (mm. of mercury)	111.8	132.5	126.8	113.4	92.0	88.0	100.0	80.7	91.0	

were not so much increased as in the animals in which shock was more profound. In the animal receiving additional trauma at the end of six hours the hyperphosphatemia increased as shock became more profound.

COMMENT

The breakdown of phosphocreatine following mechanical injury to skeletal muscle by hammer blows and by the mechanical press is probably responsible in part for the hyperphosphatemia observed in these experiments. Elevations of plasma creatine following muscle injury are also evidence that hydrolysis of phosphocreatine has occurred.[3] In the case of experimental crush injuries and possibly to a slight degree in the case of trauma by hammer blows, ischemia of the extremity is an additional factor producing breakdown of phosphocreatine. During the five hour period in which the mechanical press is on the thigh at least the major part of the blood supply to the extremity is interrupted. This ischemia and the resulting anoxia of the extremity may also cause breakdown of other organic phosphates in the tissues of the extremity with liberation of inorganic phosphate. The elevation of inorganic phosphorus was not so progressive in 2 of the animals subjected to trauma by hammer blows, although they received presumably the same amount of trauma. As shock developed after additional trauma to 1 of these animals, greater elevation of serum inorganic phosphorus was noted. This progressive increase in inorganic phosphorus as shock became more profound and the fact that marked hyperphosphatemia occurred following hemorrhage suggest that factors other than injury to muscle are contributory. The generalized anoxia and other deleterious effects of shock may be responsible for damage to tissue with breakdown of organic phosphates and liberation of inorganic phosphate.

Diminution in renal function may be partly responsible for elevation of serum inorganic phosphorus, since elevations have been shown to accompany nephritis [4] and cessation of renal function by ligation of the ureters.[5] Oliguria and elevation of blood nonprotein nitrogen have been demonstrated in cases of experimental crush injuries [1] and other types of trauma.[3a] Banaytis [6] reported hyperphosphatemia following trauma and emphasized its relation to disturbance of carbohydrate metabolism.

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Owing to the inverse relation which exists between the blood levels of phosphate and calcium ions, such elevations of phosphate will result in the withdrawal of calcium from the blood and may therefore be a factor in the production of increased permeability of the capillaries, which is believed by most investigators to occur in shock. Chambers and Zweifach [7] have shown that perfusion with calcium-free solutions produces an excessive leakiness of the walls of the capillaries. In view of these elevations of inorganic phosphate, determinations of ionized calcium are indicated in experiments of this type because of possible relations to capillary permeability and neural and muscular function in shock. Excessive inorganic phosphate may be one of the contributing so-called toxic factors in the irreversible shock which has been shown to result when extremities are subjected to trauma and prolonged ischemia.[8] Inorganic phosphate may also contribute to the renal lesions seen in clinical cases of crush syndrome, since ischemia and muscular injury of one or more extremities were present in all reported cases.

It is of interest to note that the serum inorganic phosphate levels showed some elevation in the control group of animals, subjected to anesthesia alone, and that the elevation was greater in some animals than in others. This elevation may have been related to depth of anesthesia, nutritional state and age as well as to other factors. The initial inorganic phosphate levels in all the groups appear to range rather widely. Single specimens drawn from 12 dogs under similar conditions had concentrations ranging from 3.3 to 7.9 mg. per hundred cubic centimeters, averaging 5.2 mg.

Whether or not serum inorganic phosphorus levels can be used as an index of clinical shock, either as an early sign or as a prognostic sign, will require further investigation. In the limited number of cases thus far observed the results have not been so marked as in these experiments. The greatest elevation has been noted in cases of severe muscular injury.

SUMMARY

The effects of shock produced by experimental crush injury, by hammer blows and by hemorrhage on the level of serum inorganic phosphorus have been studied.

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Serum inorganic phosphorus is elevated in shock produced by each of these methods. The time relation between this elevation of inorganic phosphate and changes in the hematocrit reading and the arterial pressure are recorded in the tables and the graphs. Hyperphosphatemia occurred early in most of the experiments in which shock was produced by experimental crush injury and by hammer blows. This early elevation was not as marked or as consistent in the experiments in which shock was produced by hemorrhage.

The possible origin of this hyperphosphatemia and its relations to some of the physiologic aspects of shock are discussed.

Johns Hopkins Hospital.

CLOT RESISTANCE IN MICE AND THE MECHANISM OF HEMOSTASIS

JOSEPH J. LALICH, M.D.
KANSAS CITY, KAN.
AND
ALFRED L. COPLEY, M.D.
NEW YORK

During previous studies we found that movement of the tail had a slight effect or none in prolonging the duration of bleeding from a wound in the tail in normal mice. In heparinized mice, however, such movements initiated bleeding which persisted several minutes.[1] We also observed that some of the mice treated with heparin or dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) [2] which had normal bleeding times continued to bleed spontaneously from the same wound after completion of the test. In an attempt to elucidate the lack of correlation between the bleeding time and this tendency to spontaneous bleeding from the same prick wound, further experiments were done. Macfarlane [3] has drawn attention to the fact that there is no satisfactory method to test the toughness of blood clots. We proposed to estimate clot resistance,[4] that is, the firmness of a clot and its adhesiveness, in a wound in the tail of a mouse by applying cuff pressure after bleeding had stopped. A cuff pressure of 75 mm. of mercury was applied proximal to the wound after the bleeding time test to ascertain if congestion of the tail would renew bleeding. Since heparin and dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) have anticoagulant action and sometimes prolong the bleeding time, these agents were used to study clot resistance. Our observations cast new light on the control of hemorrhage and therefore necessitate a discussion of the mechanism of hemostasis.

From the Hixon Laboratory for Medical Research, University of Kansas School of Medicine, Kansas City.

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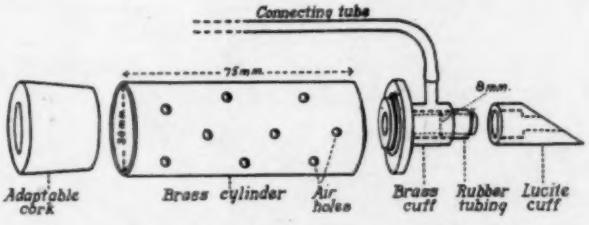
4. Copley, A. L., and Lalich, J. J.: Bleeding Time, Lymph Time and Clot Resistance in Men, J. Clin. Investigation **21**:145 (March) 1942.

METHODS

The mouse was enclosed in a brass cylinder which was suspended at an angle of approximately 40 degrees, so that the tail was immersed in a bath of physiologic solution of sodium chloride of constant temperature (37.5 C.), as previously described.[1] After the wound had been inflicted the duration of bleeding could easily be observed and timed as the blood emerged from the wound and escaped into the saline bath. At intervals varying from 0 to 466 minutes following the bleeding time tests the mice had cuff pressures of 75 mm. of mercury exerted at the base of the tail for one minute. This cuff pressure was arbitrarily chosen in order to standardize the test. When the cuff pressure was applied, the wound was observed for a renewal of bleeding. To exert cuff pressure on the mouse's tail, a brass cuff was constructed (figure). The cuff was 3.8 cm. long, with a central hole 8 mm. in diameter which was lined with surgical drain tubing. The cuff was connected to a mercury manometer with a rubber tube. The proximal part of the cuff fitted into the cylinder which held the mouse. A piece of lucite was fitted on the distal part of the cuff and kept the mouse's tail suspended.

Adult male and female mice fed Friskies dog food (Albers Milling Company, Seattle)[4a] and crushed oats were used.



Apparatus for determining clot resistance.

Three types of wounds were made on the tails of normal mice, to establish if the size of the wound would affect the bleeding time or the clot resistance. In 55 mice, 1 to 2 mm. of the tip of the tail was amputated with sharp scissors. In 98 mice, cutaneous incisions measuring 3 to 6 mm. in length and varying in depth were made on the lateral, distal portion of the tail with a razor blade. In 109 mice venous and arterial prick wounds were made in the middle portion of the tail with a pointed stylet measuring 0.5 by 1.5 mm. These 109 normal mice showed uniform results in bleeding time; hence this group served as control for subsequent experiments.

4a. Friskies Dog Food, according to the manufacturer, contains meat and bone scraps, ground wheat, soybean oil meal, ground corn, ground hulled barley, oat meal, dried skimmed milk, wheat bran, wheat germ meal 3 per cent, liver meal 3 per cent, dried beet pulp and molasses 3 per cent, fish meal 3 per cent, steamed bone meal 2 per cent, dextrin 3 per cent, charcoal 0.25 per cent, sardine oil (100 A. O. A. C. chick units of vitamin D per gram; 3,000 U. S. P. units of vitamin A per gram) 0.15 per cent, salt 0.25 per cent, iron oxide 0.125 per cent and irradiated brewers' type yeast 0.05 per cent. The guaranteed chemical analysis is as follows: protein (minimum) 22 per cent, fat (minimum) 3.5 per cent, fiber (maximum) 4 per cent, nitrogen-free extract (minimum) 45 per cent, ash (maximum) 10 per cent and moisture (maximum) 10 per cent.

One part of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin])[5] was dissolved in 1,000 parts of a 0.1 per cent solution of sodium carbonate and administered orally with a blunt 18 gage needle. The mice received daily doses of 30 to 60 mg. per kilogram of body weight for three days, and the tests were done on the fourth day. Heparin (Connaught Laboratories, University of Toronto, 110 Murray-Best units per milligram) was injected subcutaneously from 239 to 403 minutes before the tests were done. The mice received 50, 100, 200 and 400 units per 20 Gm. of body weight. Clot resistance was measured by application of a cuff pressure of 75 mm. of mercury or by observation of spontaneous bleeding. Spontaneous bleeding was manifest either when the animal was left undisturbed in the cage or as the mouse was placed in the brass cylinder for the clot resistance test. All mice

TABLE 1.—*Duration of Bleeding from Different Parts of the Tail and the Effect of Cuff Pressure on the Clot Resistance in Normal Mice*

Amputation of Tail				Cutaneous Incision 3 to 6 Mm. in Length			
Mouse Number	Duration of Bleeding, Seconds	Interval Between Bleeding and Clot Resistance Test, Min.	Effect of 75 Mm. Hg Cuff Pressure for 1 Minute	Mouse Number	Duration of Bleeding, Seconds	Interval Between Bleeding and Clot Resistance Test, Min.	Effect of 75 Mm. Hg Cuff Pressure for 1 Minute
58	189	0	—	24	30	21	—
57	44	0	—	2	91	30	—
54	7	0	+	3	137	32	+
51	56	0	+	39	58	37	—
52	30	0	+	47	85	37	+
95	43	0	+	26	88	38	+
53	45	16	+	44	51	41	+
4	..	18	—	48	186	45	+
43	41	21	—	33	430	47	+
1	..	24	—	25	97	49	—
19	..	24	+	35	62	50	—
10	..	29	—	37	76	53	—
5	..	30	—	80	102	53	—
8	..	38	+	40	98	56	—
11	..	38	—	42	174	59	—
2	..	40	+	34	205	63	+
59	665	42	—	31	53	72	+
6	...	45	—	43	288	76	—
9	...	52	+	45	105	130	+
56	704	..	..	49	609	152	+

+, bleeding; —, no bleeding.

were examined for spontaneous bleeding two or three times per hour during the first four hours following the bleeding time test. The term "bleeding time" is restricted to the value shown by the initial bleeding time test and does not include recurrent bleeding due to decreased clot resistance.

RESULTS

Table 1 shows the effect of amputation wounds and cutaneous incision wounds on the duration of blood flow and the renewal of bleeding after application of cuff pressure. Twenty mice out of each group are presented in the table.

5. Supplied by Dr. J. F. Biehn, Abbott Laboratories, North Chicago, Ill.

Bleeding times from amputation wounds varied from 7 to 704 seconds in 11 mice. A cuff pressure of 75 mm. of mercury for 1 minute provoked bleeding in 22 of the 55 mice studied. Nine mice had the cuff pressure applied after 11 to 54 minutes with a renewal of blood flow. In 7 mice pressure initiated bleeding after 0 to 24 minutes but failed on the second trial 18 to 44 minutes later. After being handled 8 to 27 minutes following amputation 4 mice bled spontaneously, but they did not show renewal of blood flow when cuff pressure was applied 23 to 84 minutes after the first handling. One mouse did not bleed when pressure was applied immediately, but bled spontaneously in the cage 28 minutes later. One mouse was tested twice, immediately and 28 minutes later, with a renewal of bleeding on both occasions. It is not possible to amputate the tip of the tail without cutting veins or the artery in some mice. Some amputation wounds had a diameter up to three times that of others, because of anatomic variations in the tip of the tail. The blood oozed from the wound when only the capillaries were cut. When larger vessels were severed the blood loss was greater and the duration of bleeding was longer.

Bleeding time from cutaneous incision wounds in 28 mice varied from 21 to 669 seconds. In 85 mice cuff pressure was applied once. Twenty-four mice out of this group showed renewed bleeding after 32 to 466 minutes, while 61 mice failed to exhibit bleeding during a similar time. Repeated clot resistance tests were done on 4 other mice. Two of them bled spontaneously after handling at 52 and 68 minutes. Cuff pressure initiated bleeding on three occasions in 1 mouse at 45, 120 and 375 minutes. The fourth mouse bled when pressure was applied at 152 and 413 minutes. The larger wounds showed an increased tendency to renewed bleeding on application of cuff pressure.

In the third group of mice a vein of the tail was cut across its long axis, about 5 cm. from the base of the tail. The bleeding times of 109 mice agreed with previous venous bleeding times.[6] Not a single mouse in this group bled spontaneously in the cage or after handling. However, after application of cuff pressure after 18 to 34 minutes renewed bleeding occurred only in 6 mice, which were excluded from further studies. The remaining 103 mice were treated either with dicoumarin or with heparin and studied subsequently.

EXPERIMENTS WITH DICOUMARIN

Three series of 10 mice received dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) in doses of 30, 50, and 60 mg. per kilogram of body weight. To one series of 30 mice 40 mg. per kilogram was administered. During the period of treatment 5 of the mice receiving 60 mg.

6. Footnotes 1 and 2.

per kilogram died; whereas only 1 mouse among those receiving 40 and 50 mg. per kilogram died. Results on 12 mice with decreased clot resistance are compiled in table 2.

TABLE 2.—*Bleeding Time and Clot Resistance in Mice Before and After Oral Administration of Dicoumarin (3,3'-Methylene-bis-[4-Hydroxycoumarin]) for Three Days*

	Control			After Treatment with Dicoumarin			
Number	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute	Mg./Kg. Daily	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute
1	57	78	—	30	54	37	+*
						109	—
2	33	15	—	30	900	19	+*
						78	+*
						128	+*
						171	+*
						244	+*
3	71	20	—	40	40	19	+
						87	—
4	102	13	—	40	30	19	+
						58	+
						139	+
						240	—*
5	29	18	—	40	75	20	+
						88	—
6	24	19	—	40	61	21	+
						48	—
7	58	16	—	40	25	22	—
						134	+†
						182	+*
						269	—*
8	31	13	—	40	80	32	+
						90	+
						250	—
9	40	14	—	50	900	13	+*
						72	—
10	54	16	—	50	123	17	+*
						31	+*
						119	—
11	34	13	—	60	30	28	+*
						103	—
12	38	20	—	60	100	24	+*
						63	+
						180	+†

+, bleeding; —, no bleeding.
* Without cuff pressure during handling.
† In the cage.

Three of the 10 mice treated with 30 mg. per kilogram exhibited bleeding during handling. One mouse had a normal bleeding time and spontaneous bleeding after 37 minutes; however, pressure after 109 minutes did not provoke a blood flow. The second mouse also had a normal bleeding time with spontaneous bleeding at 19, 77, 115, 165 and 282

minutes. The third mouse had a bleeding time longer than 15 minutes, and spontaneous bleeding occurred at 19, 78, 128, 171 and 244 minutes. A fourth mouse in this group had a bleeding time longer than 15 minutes and died before the clot resistance test could be done. The remaining 6 mice had normal bleeding times, and cuff pressure did not initiate bleeding.

Nine of the 30 mice treated with 40 mg. per kilogram had a decreased clot resistance, and 29 mice had normal bleeding times. One mouse had a bleeding time longer than 15 minutes and showed spontaneous bleeding during handling at 29 minutes. In 3 of the 9 mice cuff pressure renewed bleeding two and three times within 139 minutes. A fifth mouse had a normal clot resistance after 22 minutes but began to bleed spontaneously in the cage after 134 minutes and after 182 minutes during handling. Cuff pressure provoked bleeding in the remaining 4 mice after 19 to 32 minutes but failed to do so after 48 to 250 minutes.

Four of the 9 mice treated with 50 mg. per kilogram had a decreased clot resistance. This was observed mostly during handling of the mice. One mouse with a bleeding time longer than 15 minutes had spontaneous bleeding after 13 minutes during handling, but pressure failed to induce bleeding after 72 minutes. The second mouse had a normal bleeding time and showed spontaneous bleeding in the cage at 11, and during handling at 75 and 114 minutes. Two other mice with normal bleeding times bled spontaneously at 17, 31 and 29 minutes during handling but failed to bleed when pressure was applied after 119 and 98 minutes respectively. A fifth mouse had a bleeding time of nine minutes and died during the test. The 4 remaining mice had normal values.

Three of the 5 mice treated with 60 mg. per kilogram had a decreased clot resistance during handling. One mouse with a normal bleeding time bled spontaneously for 20 minutes in the cage and at 28 minutes during handling, but after 103 minutes pressure did not provoke bleeding. A second mouse had a normal bleeding time, bled spontaneously during handling at 24 minutes, required pressure to initiate bleeding at 63 minutes, bled in the cage after 3 hours and subsequently died of hemorrhage. The third mouse had a normal bleeding time, and pressure initiated bleeding at 20 minutes. The fourth mouse had a bleeding time longer than 15 minutes and died. The fifth mouse had a normal bleeding time and a normal clot resistance.

EXPERIMENTS WITH HEPARIN

Heparin was injected into four groups of 43 mice. Four mice received 400 units; 4 were given 100 units, and 3 had 50 units. Thirty-two mice received 200 units; the results on 15 of these mice are listed in table 3.

Seven mice which received 50 and 100 units of heparin exhibited normal bleeding time and clot resistance. Three of the 36 mice which were treated with 200 and 400 units died before studies were done.

TABLE 3.—*Comparison Between Bleeding Time and Clot Resistance in Mice Before and After Subcutaneous Injection of Two Hundred Units of Heparin per Twenty Grams of Weight*

	Before Injection			After Injection			
Number	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute	Duration of Action of Heparin Until Bleeding Time Test, Minutes	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute
1	90	25	—	301	35	10	—
						84	+
2	38	23	—	380	230	17	—
						46	+
3	50	31	—	360	900	18	+†
						97	+
4	55	34	—	342	57	19	—
						131	—
5	80	22	—	247	67	20	—
						125	+
6	117	29	—	328	780	20	—
						139	+
7	61	31	—	239	190	20	—
						149	+
8	62	12	—	350	24	22	—
						118	—
9	25	33	—	307	85	22	—
						75	+†
						160	+
10	70	23	—	263	250	28	+*
						120	+
						238	+
11	67	20	—	322	45	31	—
						145	—
12	70	29	—	323	45	31	—
						143	+
13	60	20	—	393	30	32	—
						91	+*
14	52	20	—	401	900	33	—
						65	+*
15	38	23	—	403	84	47	—
						72	+

+, bleeding; —, no bleeding.
* During handling.
† In the cage.

Twenty-six of the remaining 33 mice had a decreased clot resistance. Of these 26 mice, 4 had bleeding times longer than 15 minutes. In a fifth the bleeding time was 13 minutes, and in a sixth, 6 minutes. Clot resistance in 14 mice was normal when pressure was applied after 6 to 33 minutes, but bleeding was renewed when pressure was applied the

second time after 29 to 199 minutes. In 7 other mice, which did not bleed when pressure was applied the first time after 11 to 48 minutes, spontaneous bleeding developed during handling or in the cage during the second hour. Five more mice initially showed spontaneous bleeding during handling after 16 to 34 minutes and continued to bleed in the cage. After hemostasis occurred, subsequent bleeding in 3 of these mice was initiated by pressure after 124 to 126 minutes. The fourth mouse continued to bleed only during handling, while the fifth continued to bleed in the cage.

On macroscopic examination it was possible to observe that the punctured vein was either narrowed in diameter or apparently empty of blood in the region of the cut. When cuff pressure was applied the first time, the tail became congested without apparent widening in diameter of the injured part of the vein. Subsequently, after 30 to 120 minutes, this area dilated either without pressure or after cuff pressure was applied.

COMMENT

Whether or not a tendency to bleeding exists in an organism might be indicated by a prolonged bleeding time whenever it occurs. However, the bleeding time test is not sufficiently sensitive in most cases to indicate that a tendency to bleeding is present.[7] We believe that studies of clot resistance should be done in conjunction with the bleeding time test the better to demonstrate a tendency to bleeding. We have shown that probably the firmness of the clot and its property of adhesion to the traumatized vessels are important in maintaining hemostasis.[4] In this study we were concerned with the size of the wound and the role played by time in the formation of the clot in their relationship to clot resistance.

The Wound Thrombus.—We have already expressed the belief that both the agglutination of platelets and the conversion of fibrinogen to fibrin are responsible for the properties of the clot which seals the wounded vessels.[4] We also believe that the clot which forms in a wound is similar to or identical with a thrombus; therefore we designate such a clot as a "wound thrombus." It is still a matter of controversy whether thrombi in general can develop without injury to the endothelium[8]; however, in our studies of bleeding such injury is obvious. The original investigations on experimental thrombosis followng traumatization of

7. Copley, A. L., and Lalich, J. J.: The Influence of Blood Transfusion and Injectons of Bursa Pastoris (Shepherd's Purse) Extract on the Clot Resistance in Two Hemophiliacs, Am. J. M. Sc. **204**:665 (Nov.) 1942.

8. Silberberg, M.: The Causes and Mechanism of Thrombosis, Physiol. Rev. **18**:197 (April) 1938.

vessels by Eberth and Schimmelbusch [9] were confirmed by Welch [10] and further developed by Aschoff.[11] Eberth and Schimmelbusch observed that agglutination of platelets occurred first at the site of injury and that this was followed by coagulation of blood. Aschoff showed that retardation and not stagnation of circulating blood brings about formation of white thrombi. He suggested that the agglutination of platelets creates a condition which fosters formation of fibrin. The formation of a thrombus explains the results of our numerous observations on human beings and on mice with cutaneous wounds bleeding into physiologic solution of sodium chloride. The volume output of blood from a wound during bleeding gradually diminishes until hemostasis occurs.[12] This phenomenon is in sharp contrast to coagulation of whole mammalian blood in test tubes, where the clot does not form for a variable interval of time and then the blood coagulates rather suddenly. Therefore, formation of a clot during and after bleeding, we believe, is similar to the formation of a thrombus, which according to Aschoff initially is a white thrombus and with further growth becomes a mixed thrombus. We have differentiated between the firmness of the clot and its adhesiveness to the wound in the vessel.[4] We believe that the adhesiveness is associated with the agglutination of platelets. Eberth and Schimmelbusch suggested that the platelets undergo a viscous metamorphosis and adhere not only to each other but to the vessel wall. At present we cannot offer an explanation for the causes of firmness of a clot. However, we feel that it is mainly dependent upon the formation of the fibrin network and its properties and subsequent changes.[13]

The Wound.—We have previously suggested that variations in bleeding time may be due to differences in the size of the wound.[12] Although we were unable to control the size or the number of vessels cut, we endeavored to study this variable by inflicting different types of wounds, such as prick, incision and amputation wounds. There was a tendency to prolonged bleeding in amputation wounds and in incision wounds longer than 3 mm. Further, we were able to differentiate the type of vessels injured by observing the flow of blood.[12] The cutting of capillaries alone was indicated by the oozing of blood. The puncture of a vein or venule was manifested by the dark color

9. Eberth, J. C., and Schimmelbusch, C.: Die Thrombose nach Versuchen und Leichenbefunden, Stuttgart, Ferdinand Enke, 1888; cited by Welch.[10]

10. Welch, W. H.: Thrombosis, in Allbutt, T. C., and Rolleston, H. D.: System of Medicine, London, Macmillan & Co., 1909, vol. 6, p. 691.

11. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924, p. 253.

12. Copley and Lalich (footnotes 1 and 4).

13. Lalich, J. J., and Copley, A. L.: A Study of Clot Firmness in Viscometer Tubes, Proc. Soc. Exper. Biol. & Med., to be published.

and the larger volume output of blood. A severed artery or arteriole, on the other hand, exhibited a pulsating flow of light red blood. In the mechanism of hemostasis all types of vessels usually are involved and should be considered. Cutaneous elasticity may affect hemostasis in different ways. It is apparent that in incision wounds smaller than 3 mm. in length or in puncture wounds, the inherent elastic property of the skin can close the margins of the wound and thus exert a resistance to bleeding. In larger wounds the elasticity of the skin can produce the opposite effect, a gaping of the margins so that they offer no resistance to bleeding. In amputation wounds of the mouse's tail the factor of cutaneous elasticity apparently does not enter into consideration. In addition to the physical factors of the skin we have postulated a humoral skin factor [1] which promotes the formation of a wound thrombus.

The Influence of Cuff Pressure on the Wound Thrombus.—After injury, formation of a thrombus [9] and narrowing of the lumen of the vessel [3] bring about hemostasis. Narrowing of the capillary lumen has been repeatedly observed to be due to endothelial swelling.[14] After hemostasis is established the wound thrombus may continue to deposit fibrin and corpuscular elements. The time factor, therefore, becomes important in the subsequent maintenance of hemostasis, since a wound thrombus, like an ordinary thrombus,[15] requires time to develop fully. With widening of the lumen the force of circulation is exerted against the wound thrombus. If the wound thrombus seals a capillary or a vein this force is negligible, but when an artery is severed the systolic pressure exerts a considerable force on the thrombus. Under normal conditions the thrombus becomes sufficiently resistant in one to two hours to withstand the pressure in small arteries. By applying cuff pressure, therefore, one simulates conditions in veins and capillaries which exist normally when wound thrombi are formed in arteries. Lewis [16] demonstrated that pressures up to 70 mm. of mercury are reached in the veins of human subjects within 40 seconds after cuff pressure of 70 mm. of mercury is applied to the arm. Theoretically, then, the pressure attained in the veins and capillaries will be similar to the cuff pressure when the cuff pressure does not exceed the systolic pressure minus the pressure required to maintain a flow of blood. The pressure sufficient to maintain blood flow may vary [17] and was found to be approximately

14. Sanders, A. G.; Ebert, R. H., and Florey, H. W.: Mechanism of Capillary Contraction, Quart. J. Exper. Physiol. **30**:281 (Sept.) 1940.

15. Welch.[10] Aschoff.[11]

16. Lewis, T.: The Blood-Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

17. Copley, A. L.; Krchma, L. C., and Whitney, M. E.: Humoral Rheology: I. Viscosity Studies and Anomalous Flow Properties of Human Blood Systems with Heparin and Other Anticoagulants, J. Gen. Physiol. **26**:49 (Sept.) 1942.

20 mm. of mercury in dogs.[18] In case a higher cuff pressure is applied, a greater force is exerted on the wound thrombus. In this respect the clot resistance test is dependent on the systolic pressure. Mice have limited blood volume, and therefore loss of blood rapidly affects their systolic pressure. This was apparent in several of the mice which either stopped bleeding when the pressure was increased from 75 to 100 mm. of mercury or started to bleed when cuff pressure was reduced from 100 to 75 mm. of mercury. We found that when cuff pressure was applied during the first hour the likelihood of provoking bleeding in normal mice was greater than when the cuff pressure was applied during the next hour. There were a few mice, however, in which the time interval did not help to increase the resistance of the wound thrombus.

Normal Mice.—Our results show that amputation or incision wounds were of such dimensions that hemostasis was maintained with difficulty in some of the normal mice. In many of the mice the time of bleeding from these wounds was prolonged. Spontaneous bleeding occurred either while the mice were resting in their cages or as they were being placed in the brass cylinder. Another group began to bleed when cuff pressure was applied, indicating that in normal mice, when the wound exceeded a certain size, a wound thrombus, even during the first hour of its formation, was incapable of withstanding the added stress of cuff pressure. These findings show that even though larger wounds exhibited an increased tendency to renewed bleeding, a few of the mice with small wounds also bled repeatedly on application of pressure. Likewise, in spite of the time interval between the cessation of bleeding and the application of cuff pressure, which favored a normal clot resistance, some mice bled when the pressure was applied after 5 hours. These apparently contradictory results suggest that other factors besides the size and shape of the wound or the time elapsing between the tests, function in maintaining hemostasis. When puncture wounds were produced in veins or arteries the observed physical features of the wound were sufficiently uniform so that hemostasis was maintained. In puncture wounds the bleeding time was as previously reported,[1] and spontaneous bleeding never occurred in the 109 mice studied. Even though hemostasis was maintained under normal conditions, it was observed that the added strain of a cuff pressure of 75 mm. of mercury during the first 30 minutes following bleeding dislodged the wound thrombus and caused a renewal of bleeding in 6 of the 109 mice. These studies emphasize that experiments must be controlled before certain substances can be tested for their effect on hemostasis.

Mice Treated with Dicoumarin.—Treatment with dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) prolonged the bleeding time in

18. Dow, P., and Hamilton, W. F.: Analysis of Emptying of Segments of Arterial Reservoir, Am. J. Physiol. **127**:785 (Nov.) 1939.

some mice. Thus earlier observations were verified.[2] The clot resistance was found to be decreased in approximately 30 per cent of the mice. Spontaneous bleeding, which was never observed in the control series, occurred in many of the treated mice, either during handling or while the mice were in the cage. The mice bled when the cuff pressure was applied initially within 40 minutes and again during the first 2 hours following the renewed bleeding. Subsequent cuff pressure usually failed to renew bleeding. The observed increase in clot resistance after the second hour indicates that the time interval favors an increase in the firmness of the clot. This hypothesis was substantiated by an exploratory study after administration of dicoumarin to a patient with recurrent thrombophlebitis whose clot firmness, as determined by a test previously described,[13] was initially decreased. With time, however, it gradually increased above the firmness observed in clots from normal persons. From the normal result of a clot resistance test made 5 minutes after bleeding time in this patient had been found to be normal, it may be inferred that the adhesiveness of the wound thrombus was not impaired, although initially there was a pronounced decrease in the firmness of the clot. Nevertheless, the hemorrhagic condition induced by dicoumarin may not be solely based on prolonged coagulation and prothrombin times, or on a decreased firmness of the clot, since Bingham, Meyer and Pohle [19] found marked capillary dilatation in their dogs treated with dicoumarin. This phenomenon of widening of the vessel may furthermore contribute to the initially decreased clot resistance in the mice treated with this compound.

Mice Treated with Heparin.—Unlike the mice treated with dicoumarin, the majority of the mice given heparin did not bleed during the first 30 minutes after the bleeding time test, but after this period of time either spontaneous bleeding developed or cuff pressure provoked bleeding. It was found that more heparin is needed to prevent agglutination of platelets than to inhibit formation of fibrin.[20] It was suggested that heparin affects the platelets by acting with an unidentified substance in plasma which may be present in different concentrations in different bloods.[21] We believe, as do Best, Cowan and MacLean,[22]

19. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3,3'-Methylene-bis-(4-Hydroxycoumarin): Its Effect on Prothrombin and Coagulation Time of Blood of Dogs and Humans, Am. J. M. Sc. **202**:563 (Oct.) 1941.

20. Solandt, D. Y., and Best, C. H.: Time Relations of Heparin Action on Blood-Clotting and Platelet Agglutination, Lancet **1**:1042 (June 8) 1940.

21. Copley, A. L., and Robb, T. P.: Studies on Platelets: II. The Effect of Heparin on the Platelet Count in Vitro, Am. J. Clin. Path. **12**:416 (Aug.) 1942.

22. Best, C. H.; Cowan, C., and MacLean, D. L.: Heparin and Formation of White Thrombi, J. Physiol. **92**:20 (Feb.) 1938.

that the agglutination of platelets is due to the presence of an "adhesive agent" and not to formed fibrin. This is also evident in white thrombus formation, in which several workers were unable to demonstrate precipitation of fibrin.[23] In spite of injection of heparin Murray, Jaques, Perrett and Best [24] found that in some of their dogs thrombosis developed after injury to the blood vessel. This is also in accordance with our observations on formation of wound thrombi in mice which received excessive doses of heparin. In mice that have been given heparin growth of a thrombus will be primarily due to deposition of platelets and not to formation of fibrin. One may therefore assume that agglutination of platelets will be fostered by the skin or tissue factor [1] released by the injury. It may be postulated that as long as the platelets are not hyalinized [22] and sufficient fibrin is not deposited to form a complete mixed thrombus, heparin may act in two ways on the white thrombus. Further growth of the thrombus will be inhibited and heparin may react with the adhesive agent and thus allow disintegration of the white thrombus. We found that a time factor was necessary to allow renewed bleeding. We suggest that this is necessary so that the heparin may react with the adhesive agent. The force which is then applied by the cuff pressure dislodges the wound thrombus from its attachments to the margins of the wound.

The phenomena of bleeding time and platelet count are not generally interdependent, as MacFarlane [3] pointed out. These findings correspond with those of Copley and Robb,[25] who demonstrated that no correlation exists between bleeding time and platelet count in mice following single or repeated injections of heparin.

We have previously shown that heparin may exhaust the skin factor and that for this reason the bleeding time becomes prolonged in mice into which large amounts of heparin are injected.[1] In these animals the injured area has no more skin factor available and is therefore unable to form a white thrombus. The recurrence in heparin-treated mice of bleeding initiated with cuff pressure, or spontaneously, from several minutes to several hours afterward, responds, as we believe, to the same mechanism. Since the decreased clot resistance occurs in hemophilia,[26] it may be regarded as another feature in the produced hemophilia-like

23. Apitz, K.: Ueber den Bau jüngster Blutplättchenthromben und den Einfluss des Novirudins auf ihre Entstehung, Centralbl. f. allg. Path. u. path. Anat. **50**:9 (Nov. 10) 1930.

24. Murray, D. W. G.; Jaques, L. B.; Perrett, T. S., and Best, C. H.: Heparin and Thrombosis of Veins Following Injury, Surgery **2**:163 (Aug.) 1937.

25. Copley, A. L., and Robb, T. P.: Studies on Platelets: III. The Effect of Heparin in Vivo on the Platelet Count in Mice and Dogs, Am. J. Clin. Path. **12**:563 (Nov.) 1942.

26. Copley and Lalich (footnotes 4 and 7).

condition in heparinized mice. It has been shown that the fibrinogen is progressively but slowly converted into fibrin in both the hemophilic blood and the heparinized blood.[27] In this connection it is of interest that the clot firmness test [13] with blood clots of hemophiliacs and blood clots from rabbits treated with heparin showed the firmness to be greatly decreased. The decrease in clot firmness of blood from the heparinized animals persisted for a long time. These findings indicate not only that the attachment of a wound thrombus may become abnormal but that the firmness of the clot itself is impaired both in persons with hemophilia and in animals that have been given heparin.

SUMMARY

An apparatus was devised for studies of clot resistance in wounds of the tails of mice. The effect of incision, amputation and puncture wounds on the bleeding time and clot resistance in normal mice was studied. The clot resistance test was standardized in mice.

Following subcutaneous injections of large doses of heparin the clot resistance in most mice was found to be decreased. Only a portion of the mice treated with dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) exhibited decreased clot resistance. The clot which is formed in the wound is differentiated from a blood clot formed in vitro and is defined as a "wound thrombus." The probable mechanisms by which heparin and dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) induced a hemorrhagic tendency in mice and decreased the clot resistance and also the factors involved in hemostasis are discussed.

Welfare Island, New York.

27. Copley, A. L.: The Phenomenon of Thixotropy in Hemophilic and Heparinized Blood, Science **94**:543 (Dec. 5) 1941.

SURGICAL ANATOMY OF THE EXTERNAL CAROTID PLEXUS

ERNEST GARDNER, M.D.
STANFORD UNIVERSITY, CALIF.

Both neurologists and surgeons have given steadily increasing consideration to the pain which accompanies vascular disease. Among the varieties is atypical facial neuralgia, in which the pain is felt in the areas supplied by the external carotid artery. Section of the sensory root of the trigeminal nerve has usually failed to relieve such pain. Other attempts to relieve it have included resection of the cervicothoracic sympathetic chain at various levels and periarterial stripping of the common carotid artery near its bifurcation. It is generally believed that the autonomic nervous system is involved in the production of atypical facial neuralgia, and on this basis attempts have been made to relieve it by severing (either preganglionically or postganglionically) the motor outflow reaching the affected sites.

After the operative treatment of atypical facial neuralgia, results are not predictable, and in some cases no relief at all is obtained. Furthermore, a Horner's syndrome results from cutting the cervical sympathetic chain. Since section of the autonomic nerves accompanying the facial artery has relieved buccal neuralgia,[1] it was felt that the pain in other areas might be relieved by denervating the external carotid artery without disturbing the cervical portion of the sympathetic trunk. However, the descriptions given of the branches of the superior cervical ganglion which pass to the external carotid artery are inconsistent, and data obtained from other vertebrates have often been assumed to be true of man without attempts at substantiation. This paper discusses the anatomy of the external carotid plexus plus other features of the cervical sympathetic chain.

No attempt is made here to review the literature other than that pertinent to the present problem. Siwe [2] thoroughly dissected the con-

From the Department of Anatomy, Stanford University School of Medicine. This work, begun at Stanford University, was completed in the Department of Anatomy, Washington University School of Medicine, St. Louis. Dr. Frederick L. Reichert suggested the problem and made available a grant from the Kinney Neurological Research Fund, Stanford University School of Medicine.

1. Reichert, F. L.: Buccal Neuralgia: A Form of Atypical Facial Neuralgia of Sympathetic Origin, Arch. Surg. **41**:473-486 (Aug.) 1940.

2. Siwe, S.: The Cervical Part of the Ganglionated Cord, with Special Reference to Its Connections with the Spinal Nerves and Certain Cerebral Nerves, Am. J. Anat. **48**:479-497, 1931.

nections of the cervical portion of the sympathetic trunk in human beings. He emphasized that a multitude of anastomoses occur between the glossopharyngeal and the hypoglossal nerve and between the vagal and the sympathetic trunk. Connections of the vagus nerve with the first two cervical nerves were found to be constant. He also pointed out that the connections of the superior cervical sympathetic ganglion and the jugular ganglion of the vagus nerve may lead to a fusion of the two. Sheehan, Mulholland and Shafiroff [3] described many of the same connections in their observations on the anatomy of the carotid sinus nerve.

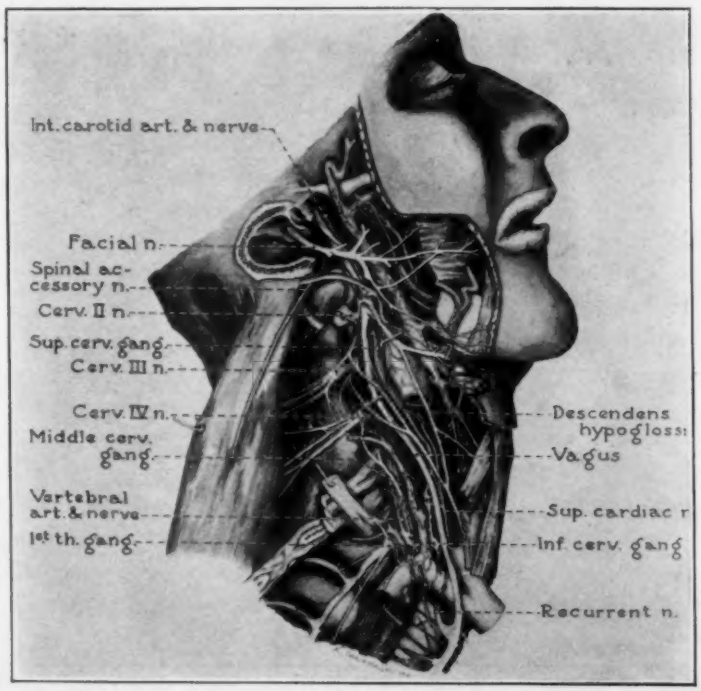


Fig. 1.—Drawing of a dissection of the right side of the head and neck. Most of the common carotid artery has been removed, and the mandible has been cut away to show the external carotid plexus. A branch entering into this plexus can be seen hooking around the hyoid branch of the superior thyroid artery. A branch of the facial nerve is seen crossing the external maxillary artery and its accompanying nerves.

MATERIALS AND METHODS

Twenty dissections were made in cadavers, and certain features were checked in student dissections at the Washington University School of Medicine, St. Louis. By the use of a fine sharp probe, small scissors and forceps, small nerve filaments could be traced for considerable distances in the connective tissue around the

3. Sheehan, D.; Mulholland, J. H., and Shafiroff, B.: Surgical Anatomy of the Carotid Sinus Nerve, Anat. Rec. **80**:431-442, 1941.

blood vessels. Where differentiation from connective tissue was needed, injection of solution of sodium chloride into the larger trunks was frequently helpful. Figures 1 and 2 are drawings of a dissection of a head and a neck which showed most of the features described in this paper.

OBSERVATIONS

The external carotid plexus is formed in a more or less constant manner. From the superior pole of the superior cervical ganglion either one branch may arise which almost immediately splits into several or

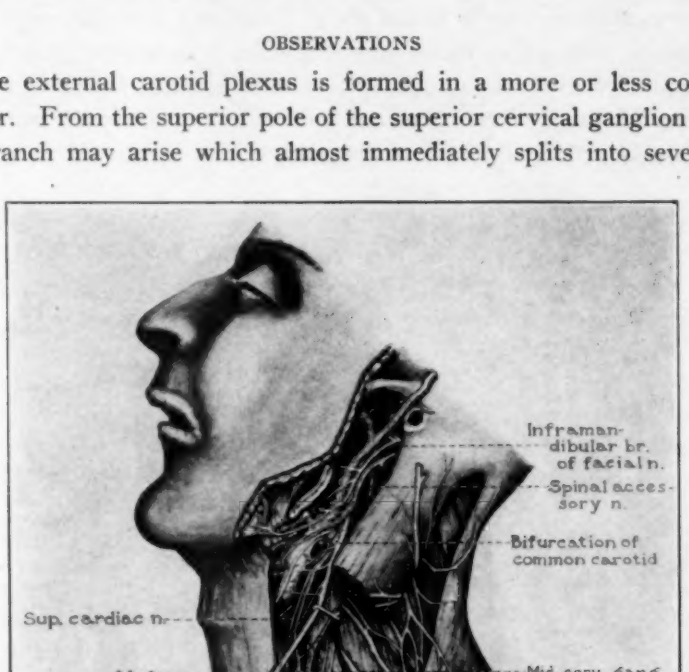


Fig. 2.—Drawing of a dissection of the left side of the head and the neck, showing the external carotid plexus with a component branch ascending from the superior thyroid artery. The deep cardiac plexus is shown encircling the left subclavian artery. A stellate ganglion is present, and lying medially is a small ganglion detached from the stellate ganglion, probably representing part of the inferior cervical ganglion.

there may be an anastomosing plexus made up of small fascicles from which three or four branches arise. One of these branches forms the twigs which enter into the formation of the intercarotid plexus described by Sheehan, Mulholland and Shafiroff. Another branch runs directly to the external carotid artery, usually to its medial side, and enters into the formation of the external carotid plexus. A third branch descends,

posterior and medial to the origin of the external carotid artery, to the superior thyroid artery. It usually anastomoses with the superior laryngeal branch of the vagus nerve and supplies the superior thyroid artery with fine filaments. Then, after passing inferior to that artery or to its hyoid branch, the nerve makes a sharp turn superiorly to ascend along the anterior surface of the external carotid artery. It supplies a few small twigs to the lingual artery, and almost immediately thereafter it anastomoses with the aforementioned branch of the superior cervical ganglion. Both branches break up into a plexus which lies in the connective tissue encircling the artery. The component branches vary in size. Filaments may be traced inferiorly to the intercarotid plexus. The occipital and ascending pharyngeal arteries are accompanied by small branches. Opposite the posterior auricular artery a gangliform enlargement is occasionally seen, the so-called temporal ganglion. The branches to the external maxillary artery are numerous, forming an anastomosing plexus which can be traced as far as the angle of the mouth. Most of the plexus appears to be derived from the branch which has hooked around the superior thyroid artery. Small filaments enter the submaxillary gland with the blood vessels, and a few join the submaxillary ganglion. As the external maxillary artery and its accompanying nerves ascend over the mandible, they are crossed at almost right angles by several large branches of the facial nerve which intertwine with these autonomic nerves.

The external carotid plexus continues superiorly to the terminal branches of the artery. Fine rami could be traced for only a short distance along the superficial temporal artery. Along the internal maxillary artery the plexus suddenly breaks up into numerous small anastomosing filaments lying in the dense connective tissue of this region. A few filaments accompanied the middle meningeal artery, and a few descended with the inferior alveolar artery into the alveolar canal of the mandible. No attempt was made to find the external superficial petrosal nerve or to trace branches to the terminal parts of the internal maxillary artery.

The branch which turns around the superior thyroid artery or its hyoid branch is nearly constant. Occasionally, it turns around the lingual artery, and a separate branch descends to the superior thyroid artery. In 4 cases the nerve communicated with the hypoglossal nerve; this was in addition to other connections which were found between the superior cervical ganglion and the hypoglossal nerve. All of Siwe's descriptions of the connections of the ganglion with neighboring nerves as well as his observations that rami communicantes from it are limited usually to the first two cervical nerves, sometimes to three and rarely to four, have been confirmed.

Figure 3 is a diagram of the external carotid plexus plus other branches of the cervical chain. The origin of the vertebral nerve is shown. This is a large nerve arising from the inferior cervical or the stellate ganglion, which crosses the vertebral artery dorsally from the lateral to the medial side. According to Siwe it joins the sixth or the seventh cervical nerve and is a ramus communicans almost entirely separate from the plexus along the vertebral artery. This vascular plexus is continuous with the subclavian plexus, and as it ascends along

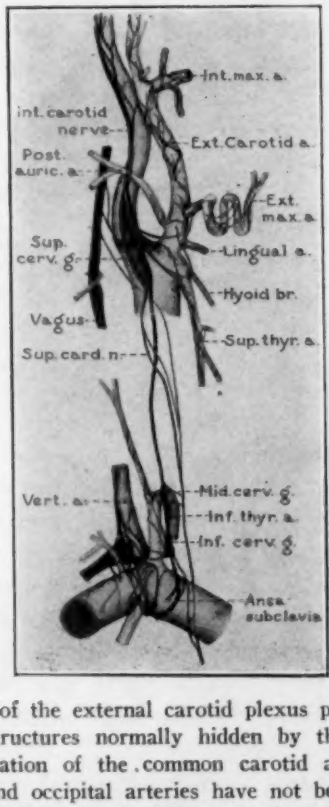


Fig. 3.—A diagram of the external carotid plexus plus other branches of the cervical chain. The structures normally hidden by the arteries are shown in gray. Only the bifurcation of the common carotid artery is shown, and the ascending pharyngeal and occipital arteries have not been indicated. The union of the superior cardiac branches of the vagal and sympathetic trunks is shown. The intercarotid plexus is also shown, but the carotid sinus nerve and other branches of the glossopharyngeal nerve have not been indicated.

the vertebral artery it connects with each of the cervical nerves. Presumably it continues to the basilar artery.

The superior part of the common carotid artery receives a few twigs from the intercarotid plexus. Filaments from the middle and inferior cervical ganglions are also distributed to the common carotid artery and

form a rather sparse plexus. It is not possible macroscopically to trace a continuous plexus along the common carotid artery from its origin to its termination. Nor is it possible to trace a plexus from the common to the external carotid artery. Such longitudinal connections may exist in other vertebrates, but if they are present in man, other methods are necessary to demonstrate them. The superior cardiac nerves are sometimes embedded in the loose connective tissue around the common carotid artery for a part of their course.

COMMENT

At first glance it is difficult to understand why axons destined for distribution to the face should descend as far as the superior thyroid artery before returning to the area they supply. The explanation may be embryologic, based on the distribution of axons to the external carotid plexus before the thyroid gland is completely formed. When the gland descends into the neck, this particular branch is carried inferiorly in much the same manner that the recurrent laryngeal nerves are carried inferiorly with the aorta and the subclavian artery. Naturally, the branch passing directly to the external carotid artery is not affected by this descent. The hooking of this nerve around the superior thyroid artery explains Frazier's [4] observation that a ligature applied to the superior thyroid artery may cause pain referred to the trigeminal area.

Periarterial stripping of the common carotid artery near its bifurcation has been done in attempts to relieve atypical facial neuralgia. If the purpose of this operation was denervation of the external carotid artery, then reasons for its failure are obvious. The external and common carotid plexuses are not directly continuous. Even if microscopic connections do exist, the external carotid artery will receive but a small fraction of its total supply from them. Denervation may be possible by periarterial stripping of the external carotid artery near its origin. Cutting the same branches as they arise from the superior cervical sympathetic ganglion will achieve the same results.

Although the autonomic nervous system is involved in the production of pain along the external carotid artery,[5] the sensation of pain is transmitted by nervous pathways to cell bodies the locations of which have not

4. Frazier, C. H.: Atypical Neuralgia, Arch. Neurol. & Psychiat. **19**:650-659 (April) 1928.

5. Davis, L., and Pollock, L. J.: The Role of the Sympathetic Nervous System in the Production of Pain in the Head, Arch. Neurol. & Psychiat. **27**: 282-293 (Feb.) 1932. Fay, T.: Atypical Facial Neuralgias: A Syndrome of Vascular Pain, Ann. Otol., Rhin. & Laryng. **4**:1032-1062, 1932. Peet, M. M.: The Role of the Sympathetic Nervous System in Painful Diseases of the Face, Arch. Neurol. & Psychiat. **22**:313-321 (Aug.) 1929.

as yet been determined with any certainty. Helson [6] studied patients in whom the sensory root of the trigeminal nerve had been sectioned for trigeminal neuralgia. He reported that there remained a perception of deep pressure and of gross changes in temperature which evidently was not transmitted by the facial nerve. It is evident that an understanding of these intricate nervous pathways awaits further and intensive studies by microscopic and experimental methods.

SUMMARY

The anatomy of the external carotid plexus plus other features of the cervical sympathetic chain has been studied in 20 dissections in cadavers. Of several branches arising from the superior pole of the superior cervical ganglion, two enter into the formation of the external carotid plexus. One goes directly to the external carotid artery. The other descends, turns sharply around the superior thyroid artery and ascends to anastomose with the previous branch. Filaments from the plexus formed by these two branches accompany all the branches of the external carotid artery.

The external carotid plexus is not directly continuous with the common carotid plexus. The arrangement is such that periarterial stripping of the external carotid artery near its origin would probably denervate the entire artery. The relation of such denervation to atypical facial neuralgia is discussed.

Department of Anatomy, Stanford University, California.

6. Helson, H.: The Part Played by the Sympathetic System as an Afferent Mechanism in the Region of the Trigeminus, Brain **55**:114-121, 1932.

FREE GRAFT OVER A VITALLIUM TUBE FOR BRIDGING A GAP IN THE COMMON BILE DUCT OF THE DOG

JERE W. LORD JR., M.D.
AND
ARTHUR I. CHENOWETH, M.D.
NEW YORK

In July 1941 Pearse [1] reported on the use of a vitallium [2] tube for the relief of stricture of the common bile duct in a group of 3 patients. His work was first carried out in dogs, and the technic was subsequently applied to human beings. Pearse drew the following conclusions:

1. A vitallium tube does not form stones or deposits in the presence of bile.

2. No pathologic changes occur in the common bile duct as a result of the contiguity of the metal tube.

3. A holder (or flange) attached to the side of the vitallium tube and protruding through the anastomosis is important in preventing the tube from slipping down the common bile duct.

4. The 3 patients in whom it had been used and in whom the ends of the common bile duct were anastomosed over the vitallium tube had remained well clinically.

More recently Pearse [3] made a supplementary report in which he discussed the use of a wide variety of vitallium tubes in benign and malignant strictures of the common duct and reported Zinninger's case of pancreatic fistula cured by implantation of the pancreatic duct over a vitallium tube into the stomach. One significant problem was stated by the author to have remained unsolved, that is, the question of how to bridge a gap in the common bile duct with a vitallium tube. He suggested the mobilization of the duodenum and the pancreas so that the duct could be moved to the hepatic fossa but recognized the fact

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From the Department of Surgery, New York Hospital and Cornell University Medical College.

1. Pearse, H. E.: Benign Stricture of the Bile Ducts Treated with a Vitallium Tube, Surgery **10**:37-44, 1941.

2. The approximate composition of vitallium is cobalt 65 per cent, chromium 30 per cent and molybdenum 5 per cent.

3. Pearse, H. E.: Vitallium Tubes in Biliary Surgery, Ann. Surg. **115**:1031-1042, 1942.

that this cannot always be done. Clute [4] in a patient with a stricture of the common duct was able to bridge a 2 cm. gap in the duct by bringing the omentum around the bare vitallium tube, the ends of which had been inserted into the separated ends of the common bile duct.

In January 1942 we began a series of experiments in the dog to determine whether a gap in the common bile duct could be bridged by means of a free transplant of peritoneum, vein or fascia over a vitallium tube. After six months of experimentation the following conclusions have been established:

1. Fascia from the anterior rectus sheath makes an ideal graft; in our animals these transplants were satisfactory in 100 per cent of cases.

2. Venous grafts are less dependable; in 4 out of 10 animals there was either significant leakage of bile or absorption of the graft.

3. Peritoneal grafts are not reliable; in 4 of 5 experiments such a graft failed, seeming to vanish by the third week, with the result that there was leakage of bile, obstruction to the duct, or both.

METHOD

Twenty-four normal mongrel dogs were operated on under anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium), and a graft from one of three sites was fashioned into a cuff around a straight vitallium tube (fig. 1). Two sizes of tubes were used, and in some instances there was a holder attached (fig. 2). An upper right rectus incision was used, and fascial grafts were taken from a strip in the anterior rectus sheath. A segment of the right femoral vein was used for the free venous transplants, and a strip of parietal peritoneum was taken from the edge of the wound when peritoneal grafts were used. Arterial silk was used as the suture material in all experiments.

The animals were killed at approximate intervals of fifteen, thirty, sixty and ninety days postoperatively. A few of the dogs died of bronchopneumonia during the first two postoperative weeks, and exploratory operations were performed on 2 animals at the end of the first week. Specimens of the common bile duct with the graft and vitallium tube were examined grossly and microscopically.

In general, fascia is easy to handle and can be fashioned without difficulty into a snugly fitting cuff around a vitallium tube. A continuous arterial silk suture was used to approximate the fascial edges. Lateral slits were made in the fascia at the holder in order to obtain a satisfactory approximation. In some animals the fascia was anastomosed to the common bile duct with three stay sutures and then the edges were joined by a continuous silk suture from stay to stay. In 1 dog stay sutures only were used, and they proved perfectly adequate.

TYPICAL PROTOCOLS

Dog 1.—A female animal weighing 53 pounds (24 Kg.) was subjected to a fascial graft over a small vitallium tube with a holder on March 16, 1942. The postoperative course was uneventful, the stools being brown on all occasions, and

4. Clute, H. M.: Bile-Duct Reconstruction with Vitallium Tubes: Report of a Case, New England J. Med. **226**:484-487, 1942.

no icterus was noted at any time. On the fortieth postoperative day the animal gave birth to a litter of four puppies. After the puppies had been weaned the dog was killed on the ninety-third postoperative day, while in a state of excellent health. Autopsy showed the vitallium tube to be in place without evidence of encrustation or deposits. The fascial graft had healed well, and there was no significant dilatation of the hepatic ducts above the operative site.

Dog 2.—A male animal weighing 49 pounds (22.2 Kg.) was operated on on Feb. 10, 1942, and a fascial graft over a large vitallium tube with a holder was carried out. The dog remained in excellent health, and on May 12, 1942, the

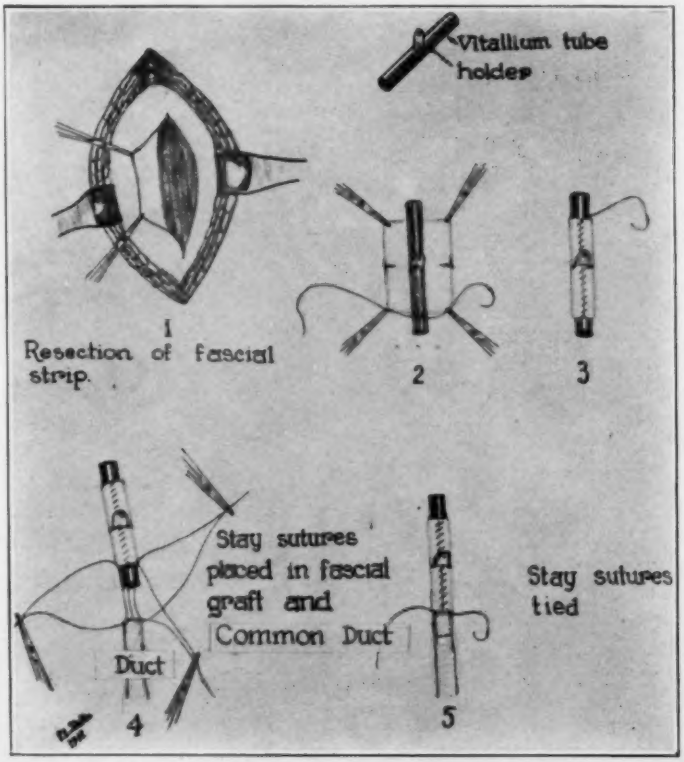

Fig. 1.—Diagram showing the various steps in the construction of a fascial graft and its anastomosis to the common bile duct over a vitallium tube with holder: *1*, a strip of fascia is resected from the anterior rectus sheath. *2* and *3*, the fascial strip is fashioned into a cuff around the vitallium tube by means of a continuous arterial silk suture; lateral slits are made at the point where the holder penetrates the cuff. *4*, stay sutures of arterial silk have been placed through the end of the common duct and fascial graft. *5*, the anastomosis of one end of the duct to the graft is completed by means of a continuous arterial silk suture; it was found that the continuous suture was not necessary.

ninety-first postoperative day, the common bile duct was resected and a cholecystogastrostomy performed. There was no dilatation of the common bile duct, and

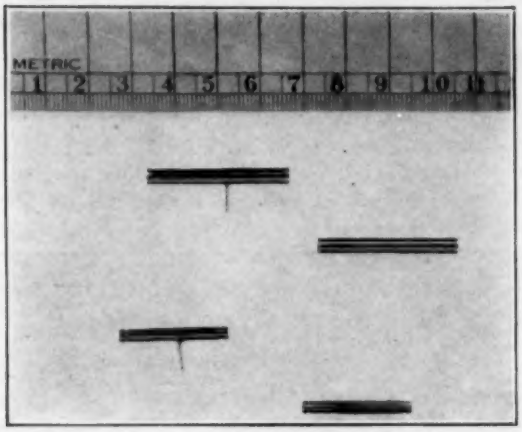

Fig. 2.—The two sizes of vitallium tubes used in this study. A holder was attached to some of the tubes.

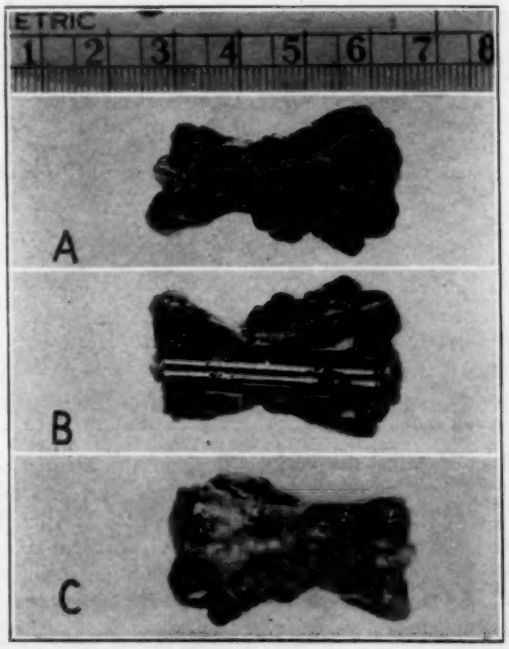

Fig. 3.—*A*, the resected common bile duct with fascial graft is viewed externally. *B*, the specimen has been opened with the vitallium tube in situ. *C*, the vitallium tube has been removed, and the fascial graft is evident between the ends of the common duct, which are glistening. Some of the silk sutures are visible.

the fascial graft had healed perfectly. It had shrunk in length, however, being only 6 mm. long instead of the original 12 mm. The vitallium tube had discrete areas of yellowish brown, granular, soft deposits both on the outside and on the inside. These deposits, which measured 1 mm. in thickness, could easily be scraped

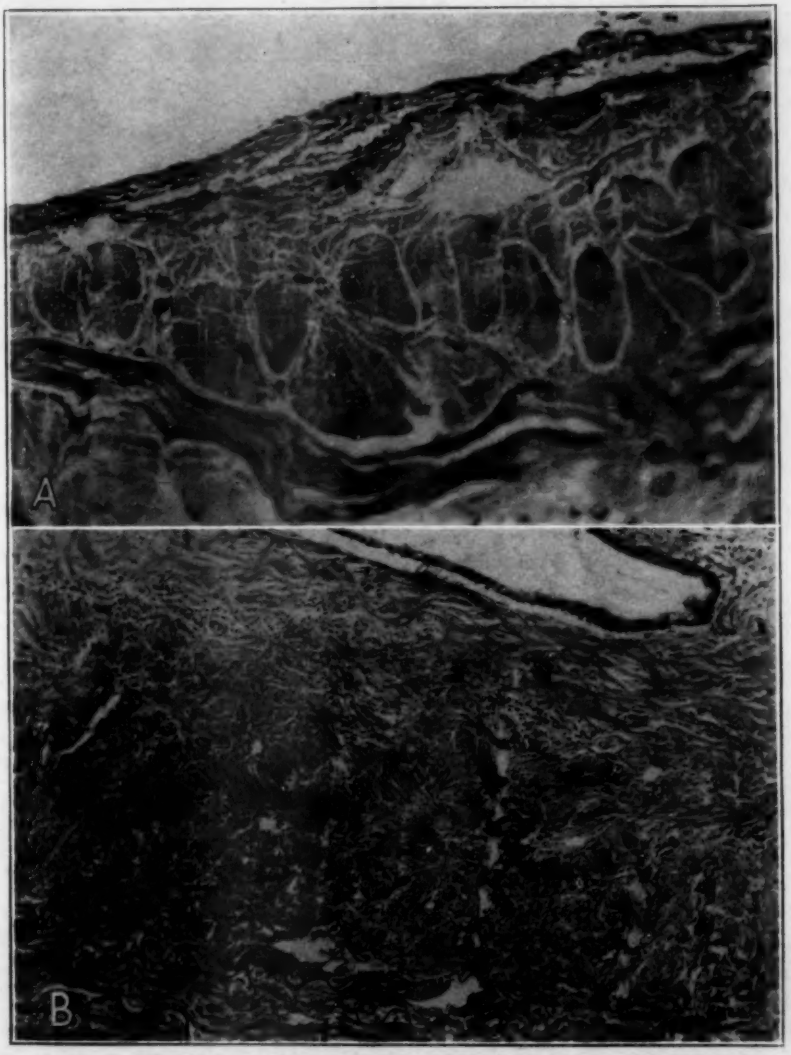

Fig. 4.—*A*, photomicrograph of a fascial graft of dog 2, showing no epithelium on the inner surface. *B*, photomicrograph of a venous graft, showing the columnar epithelium to line its inner surface. At the bottom of the film elastic fibers are in evidence.

away (fig. 3). A photomicrograph of the specimen revealed that no epithelium had grown along the graft to line its inner surface. This finding is in contrast to

the experience with venous grafts, in which epithelium does line the vein in some cases (fig. 4).

RESULTS

Fascial Grafts.—There were 9 dogs in this group. In every instance the fascial graft took satisfactorily, and at no time was there any evidence

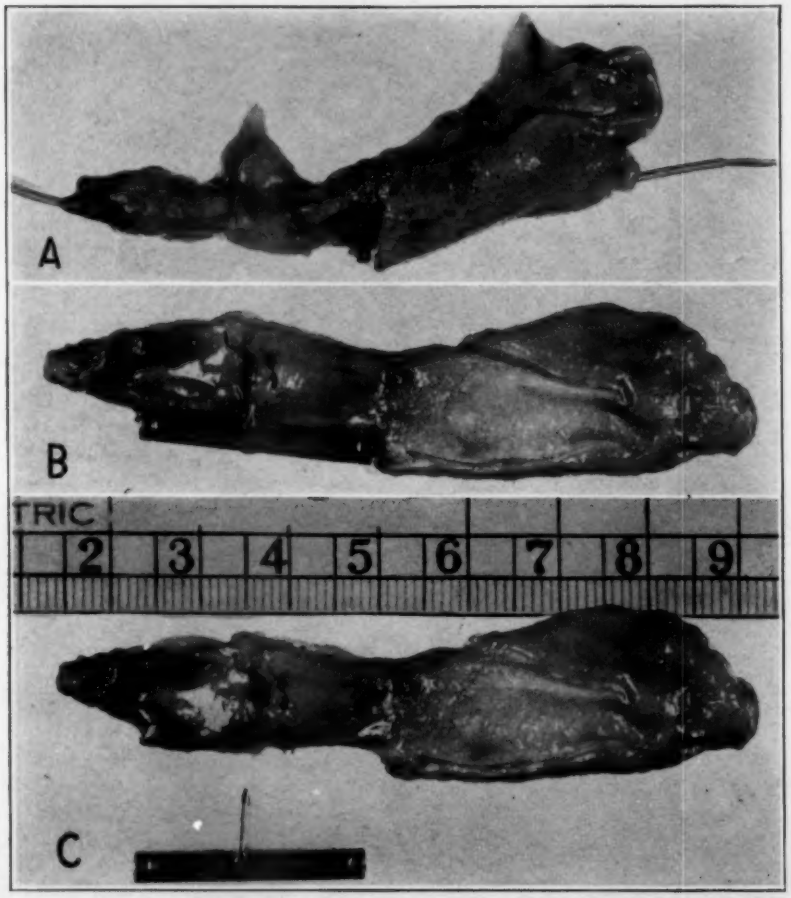

Fig. 5.—*A,* the specimen includes the common bile duct and the wall of the duodenum. A probe passes from the ampulla of Vater through the duct. The holder of the vitallium tube can be seen. *B,* the specimen has been opened, and the venous graft has evidently shrunk to 2 or 3 mm. The two rows of silk sutures are in evidence. *C,* the vitallium tube has been removed and is free from deposit. The mucosa of the common duct is glistening and shows no evidence of trauma caused by the vitallium tube.

of biliary leakage. In 2 dogs stricture of the fascial graft developed because of slipping of the vitallium tube. Epithelization of the graft did not occur in any animal.

Venous Grafts.—In 10 dogs a graft from the femoral vein was used to bridge a gap in the common bile duct over a vitallium tube. Of the 4 dogs in which the procedure was not successful, in 2 a slough of the venous graft developed, with subsequent obstruction to the common bile duct, and in the other 2 leakage of bile occurred during the first postoperative week, resulting in walled-off collections of bile. In these 2 animals the venous graft, in spite of careful suturing, became loose around the vitallium tube, with the result that gross apertures were evident. On the other hand, in the remaining 6 dogs no jaundice or leak developed, and the animals maintained a state of good health throughout the experiment. During the postoperative period 5 of the 6 animals were killed, 1 after two weeks, 3 after two months and 1 after ninety-two days. The grafts had taken well, and the only outstanding abnormality was that in 2 of the 5 grafts a pronounced shrinkage had occurred in the vein, so that the two suture lines had practically joined, being only 2 mm. apart (fig. 5). Microscopic study revealed that epithelization did occur over the inner surface of some of the venous grafts during the first ninety-two postoperative days.

Peritoneal Grafts.—In 5 dogs peritoneal grafts were made in a similar fashion, and in 4 animals the graft sloughed, with consequent leakage, peritonitis and death. The remaining graft was examined at the end of two weeks, and it appeared to be normal.

COMMENT

Most patients with strictures of the common bile duct will be amenable to the insertion of vitallium tubes with end to end anastomosis of the duct over the tube, but there will be an occasional case (for example, case 2 in Pearse's original paper [1] and Clute's case [4]) in which the surgeon will not be able to bring the ends of the duct into apposition, and it will be this group of patients in which a fascial graft over a vitallium tube with a holder should be employed. The greatest length of the graft possible remains a matter of speculation since in all of the dogs the length of the graft was limited by the length of the tube, because the ends of the vitallium tube must protrude beyond the graft, and hence beyond the two anastomotic lines. Therefore the grafts in these experiments varied between 1 and 2 cm. in length. Elsewhere [5] fascial grafts 4 cm. long have been used to bridge a gap in the jejunum over a vitallium tube 6.5 cm. long.

In the urinary tract, fascial grafts become lined with transitional epithelium,[6] but in none of the fascial grafts of the common bile duct did the epithelium grow down to line the inner surface of the graft.

5. Lord, J. W., Jr., and Stefko, P. L.: Unpublished data.

6. Lord, J. W., Jr.; Stefko, P. L., and Stevens, A. R.: On Bridging a Gap in the Ureter by Means of a Free Fascial Transplant over a Straight Vitallium Tube: An Experimental Study, J. Urol., to be published.

The vital importance of employing a vitallium tube with a holder is evident in view of the stricture which occurred in a dog in the series some twenty days postoperatively; the tube had passed into the duodenum early in the postoperative course. Tubes without holders were used in 14 animals, and obstructive jaundice secondary to slipping of the tube and stricture formation occurred in 4.

In 2 instances in this series of experiments, once in a fascial graft and once in a venous graft, the vitallium tubes showed yellowish brown amorphous deposits 1 mm. thick. In neither case did the deposits cause obstruction to the flow of bile. In the animal in which fascia had been used the tube was examined ninety-one days postoperatively, while in the dog with the venous graft the specimen was examined on the sixty-sixth postoperative day. Dr. Pearse informed us [7] that in no case has he ever found any deposits on a vitallium tube, and his experiments were continued for two years on dogs and for nine months on a human subject. We are at a loss to explain the deposits on the vitallium tubes in 2 of our dogs. Whether they would have eventually accumulated to the point of complete occlusion of the tube is a matter of conjecture. Clinical experience, as it enlarges, may confirm this finding as an unfortunate though unusual occurrence.

The principle of the permanent rigid tube to prevent the recurrence of a stricture, as established by Pearse, is a sound one and is a significant advance in the operative treatment of stricture of the common bile duct. However, even though vitallium far surpasses any other substance heretofore employed for this purpose, it may be hoped that some substance will be found which will be more pliable and even more inert.

CONCLUSIONS

1. By means of a free fascial graft from the anterior rectus sheath, fashioned into a cuff around a straight vitallium tube with a holder, a gap in the common bile duct of the dog can be bridged with uniform success.

2. Venous grafts are only moderately successful, for in 40 per cent of the animals used in the experiments reported here bile leaked during the first week after operation and/or sloughing of the graft with formation of a stricture occurred. Also, venous grafts which take satisfactorily tend to shrink more rapidly and completely than fascial grafts.

3. Free peritoneal grafts should not be employed, since they sloughed in 4 out of 5 instances.

The Austenal Laboratories, New York, through Mr. J. J. Erdmann, supplied the vitallium tubes used in these experiments.

7. Pearse, H. E.: Personal communication to the authors.

OPERATIVE TREATMENT OF CANCER OF THE LARGE BOWEL WITHOUT COLOSTOMY

W. WAYNE BABCOCK, M.D.
AND
HARRY E. BACON, M.D.
PHILADELPHIA

Carcinoma of the large bowel is the second most common and the most curable of all internal cancers. Although it is usually easier to diagnose than other internal cancers, delay in recognition and radical treatment makes it responsible for about one fourth of all deaths from malignant disease. Over 60 per cent of cancers of the large bowel may be accurately and instantly diagnosed by palpation with the finger or by inspection through a proctoscope, yet a large percentage of patients are treated for other conditions because these simple examinations are not made. Commonly a roentgen examination is ordered, which usually fails to delineate a cancer of the pelvic colon. On the basis of this negative evidence, the patient then may be treated for hemorrhoids, anal fissure, colitis, prostatitis, spastic colon or other conditions until he falls into the hands of some one who is perhaps less scientific but who first of all depends on an examining finger. Unfortunately, most of the lesions now seen by surgeons have long passed the early papular or polypoid stage, and their malignancy is clearly obvious without biopsy. With earlier diagnoses, which entail more attention to the less conspicuous lesions, the rate of curability of intestinal carcinoma could be doubled.

At this time we wish to discuss particularly the morbidity of operations for malignancy of the large bowel. Unquestionably, the greatest mental distress and physical discomfort that follow the operation are due to colostomy. The first question the patient usually asks is, "Will I be left with an intestinal opening on my abdomen for the balance of my life?" Surgeons tend to be ritualists and to follow the operative pattern of the period. They leave an ugly abdominal scar because a McBurney or a Bassini introduced the incision. For years a colostomy with any proctosigmoidectomy has been sacrosanct. In defense of the pattern it must be admitted that an operation for cancer

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From the Surgical Department of Temple University.

Read before the Section on Gastro-Enterology and Proctology at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1942.

of the lower part of the bowel which does not leave the patient with a colostomy opening cannot be approved fully unless one is assured that it will not markedly increase the mortality, that it will be equally radical and that the perineal opening will be found advantageous after the operation.

Does colostomy necessarily reduce the danger of the operation? Recent mortality statistics from various clinics where colostomy is an essential part of the operation, although not entirely comparable, suggest that the colostomy does not add to the safety of the operation. Since 1930, when we began to eliminate routinely establishment of a permanent abdominal colostomy opening in operating for removable carcinoma of the large bowel, we have had 367 operations for this condition on patients from 23 to 88 years of age. Two hundred and eight were single stage resections for carcinoma of the rectosigmoid or anus. These include 99 abdominoperineal proctosigmoidectomies, 99 perineal proctectomies or proctosigmoidectomies and 9 resections with primary end to end anastomosis. Nearly all were one stage procedures. Of the 208 patients, 24 died in the hospital, a mortality of 11.6 per cent. In 1939 technical improvements came into routine use, including improvements in anesthesia, use of nonirritating suction or of dependent drains and modifications to insure a more functional anal opening. One hundred and sixty-one patients have had operations for cancer of the large bowel since 1939, with 11 deaths in the hospital, or a mortality of 6.8 per cent. Ten, or 6.2 per cent, were found to have inoperable lesions; 150 (93.3 per cent) had radical resections. Twenty of those on whom resection was done had early metastatic carcinoma of the liver; 4 had invasion of the small intestine, 6 of the uterus and others of the ureter, vagina, prostate or abdominal wall, requiring resection or removal. One hundred and seven had resections involving the pelvic colon, with 7 deaths, a mortality of 6.5 per cent.

If the colostomy is essential to render an abdominoperineal proctosigmoidectomy radical, then it should not be possible after the operation to move the colostomy fistula to the perineum. In 12 patients we have found no especial difficulty in moving to the perineum the opening left after a Miles operation or some other procedure. With the exception of a feeble man of 74 with metastatic carcinoma of the lung who died in the hospital after a stage operation, all these patients recovered from the operation. Our observations have convinced us that operations without an abdominal colostomy may be fully as radical as those routinely done with it. Of 100 patients traced after leaving the hospital, 81 lived one to five years or more, 38 five to ten years and 19 ten years or more.

Is the perineal opening, even without sphincter control, worth while? Our best evidence comes from the 11 patients for whom an abdominal colostomy fistula has been moved to the perineum after it had been

present from a short time up to eleven years. From these patients we have learned that the discharge of offensive gas is much less evident from a perineal opening, even when the anus and sphincters have been removed. Apparently this is due in part to compression by the buttocks. The patients tell us that the perineal opening is more convenient and easier to care for and that evacuations are more satisfactory and less frequent. A physician who had had a Miles operation performed eleven years before was so troubled by the noisy escapes of odorous gas every time he bent over that he carried with him an irrigating outfit so that he could empty the bowel several times a day, and finally contemplated suicide. He left the hospital ten days after the transplantation operation and reports that he now can go about without a pad or other protection and that it is necessary to irrigate the lower part of the bowel only once in two or three days. A second patient had lost her position in a bank on account of the odorous gas escaping from the colostomy opening. The transfer of the abdominal opening to the perineum overcame this handicap. A laundress was refused work on account of the abdominal opening. A fourth patient had extreme intestinal prolapse and hernia associated with the colostomy opening, which required hours of attention daily. In a woman of 26 the colostomy had introduced a problem in connection with her approaching marriage. The transfer of the opening has probably relieved a marital problem for others. Each one of the 11 patients considered the transplantation of the fistula to the perineum of great advantage.

Five to 10 per cent of patients with a perineal colostomy opening without sphincter control require no local protection or change in diet except during periods of diarrhea. To limit soiling, about 85 per cent require an emptying of the colon by an enema or a quickly acting laxative every third or fourth day. By this expedient the majority dispense with use of a protective pad most or part of the time. However, with over 85 per cent of cancers of the large bowel the pelvic floor is not involved, and a functional anus with its sphincters may be retained safely instead of being sacrificed, as in the conventional operations now used. Many observations indicate that the lymphatic extension of cancer of the rectosigmoid is cephalad, not caudad. While a wide removal of intestinal and lymphatic tissue is imperative on a level with and proximal to the growth, a much less extensive resection below the tumor is required. Therefore, with a rectal carcinoma 7 cm.[1] or more above the pelvic floor, the anus and functional sphincters may be retained.

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1. Some authors (Westhues, H.: Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms, Leipzig, George Thieme, 1934. Gilchrist, R. K., and David, V. C.: Lymphatic Spread of Carcinoma of the Rectum, Ann. Surg. **108**:621 [Oct.] 1938) present evidence for 5 cm. as the limit of safety.

In any case, the abdominal liberation of bowel, mesentery and lymphatics resembles that of the Miles operation, except that a left oblique inguinal incision usually is employed. To reduce the bulk of tissue to be delivered through the perineum and to afford space for the formation of a pelvic diaphragm, the liberated bowel may be divided by cautery between double clamps of the de Martel type and removed. With cancers low in the pelvis this is not feasible, and there is tied about the loop of freed bowel at the level to be used for the perineal anus a folded gauze tape, the ends of which are packed against the floor of the pelvis before the abdomen is closed. It is essential that sufficient vascular sigmoid be liberated (12 cm., or 5 inches) to reach from the posterior pelvic brim through the perineum. Viability is determined by observing pulsating arteries or by the character of bleeding when the small vessels on the surface of the bowel are incised. If necessary, the descending colon is slid to a lower position, after its lateral peritoneal leaflet has been divided. If the bowel is resected between clamps through an abdominal incision, the proximal and distal ends are encased in stockinet tubing and placed on the floor of the pelvis, a pelvic diaphragm is formed, and the abdomen is closed. With the patient in lithotomy position, an anterior perineal delivery of the ends of the bowel through an incision of the Young prostatic type gives a better anal opening, since the bulk of the anal muscles lies posterior to the anus. This incision also facilitates the resection of an invaded prostate. Through the opening anterior to the anus the stockinet ends are grasped and used to deliver the ends of rectum and sigmoid. The lower end of the rectum is divided by cautery just above the sphincters. A Payr clamp is passed through the anus and caused to grasp the sigmoid above its clamp, which is burned off by cautery. The Payr clamp and end of the sigmoid are withdrawn through the anus, and the perineal incision is closed with interrupted layer sutures of fine alloy steel wire. Through a median stab wound near the tip of the coccyx a curved, perforated glass sacral drain is inserted (fig. 1). If the rectum is attached posteriorly, a median cutaneous incision is made from the posterior border of the closed anus and deepened along the side of the coccyx into the pelvic cavity. The stockinet covering the clamped ends of the bowel is then grasped, the bowel is liberated and the ends are pulled through the perineum. The asepticized rectal end is divided by cautery just above the sphincters, the anus is split posteriorly and the end of the sigmoid laid in the anal groove. A perforated curved glass drain is inserted along the sacrum, to be removed after twenty-four hours, and the perineal wound is partly closed with buried and superficial sutures of 32 B. & S. gage alloy steel wire (fig. 2).

A variation of the operation is to pull through the perineum the unopened loop of rectosigmoid by a tape previously tied about the sigmoid

at the level where the new anus will be formed. The posterior incision leaves an anus of keyhole shape which in two months or more may be improved, if desired, by turning forward a U-shaped flap formed exter-

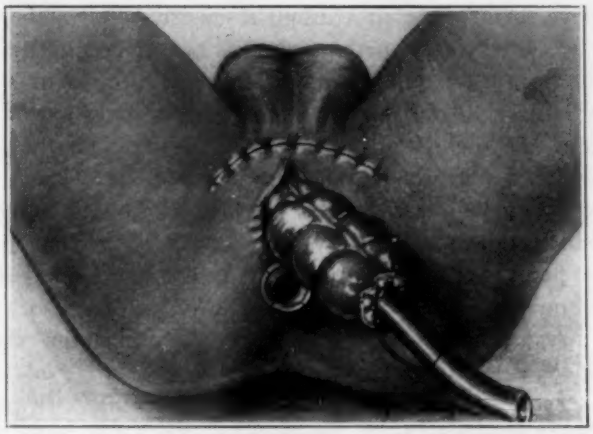

Fig. 1.—The rectum and part of the sigmoid have been liberated and resected between short clamps through an abdominal incision, and the clamped ends have been delivered and further resected through an anterior curved perineal incision. The sigmoid end has been brought through the anus, which has been split anteriorly, and a rectal tube has been tied in. A perforated curved glass drain is inserted along the sacrum through a stab wound at the right side of the coccyx.

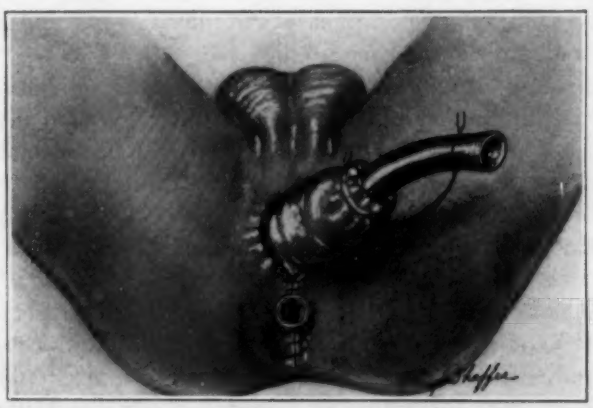

Fig. 2.—The loop of cancerous rectum and sigmoid liberated through the abdomen has been delivered through a midline post anal perineal incision. This loop of bowel has been divided through the sigmoid and also just above the sphincters, the sigmoid end has been placed in the gutter formed by the split anus and a rectal tube has been tied in.

nally along the posterior cutaneous margins of the exposed sigmoid. The sphincters, perineal muscles and skin are united under the flap with interrupted wire sutures. If an anterior spur has formed where

the sigmoid joins the anus, this should be split anteriorly and sutured before the U-shaped flap of bowel is raised. Except when a plastic operation is performed a rectal tube is tied in the protruding sigmoid, which should not be sutured to the perineum. A week later, when adhesions have formed, the protruding insensitive end of the sigmoid is burned off by cautery. The patient often is out of bed by the sixth day and in condition to leave the hospital by the twelfth or the fourteenth day.

For low-lying anal and rectal cancers a wide excision of the pelvic floor is made, and the withdrawn sigmoid is placed in the position of the anus. Such a perineal or posterior resection is a useful operation for the aged and very obese and for some patients with involvement of the vagina and prostate. It has the great disadvantage that it is difficult after any extensive perineal rectosigmoid resection to bring the divided end of the bowel to the perineum without interfering with its blood supply. As a result there is danger of pelvic infection, and a retracted and cicatricial bowel opening often forms.

The preservation of the sphincters is more difficult with the perineal resection and, of course, is not to be attempted for a low-lying carcinoma. We have preserved functional sphincters by using an interrupted long medial perineal incision to expose the rectum just above the sphincters, the rectum being divided between ligatures. The first incision is then completed vertically through the anus, the margins retracted and the rectosigmoid widely liberated and delivered through the split anus. This procedure is followed by reconstruction of the perineum with drainage. In all these operations a preliminary careful cleansing and packing of the rectum with antiseptic gauze is employed.

A secondary perineal hernia, for which a plastic operation may be done if the condition is annoying, develops after excision of the pelvic floor in about 5 per cent of perineal excisions. A moist opening from mucous prolapse may be corrected by linear cauterization, which may be done nearly painlessly as an office procedure. If there is a tendency to contraction of the new opening, the patient is given a set of test tubes to be used as dilators.

For resections of the colon above the pelvis, our present tendency is toward resection with end to end anastomosis and complemental appendicostomy or enterostomy well proximal to the anastomosis. With the development of nonirritating suction drains for the peritoneum and a satisfactory one clamp method of end to end anastomosis with fine alloy steel wire sutures, the mortality subsequent to the anastomosis now compares favorably in our experience with that associated with the Paul-Mikulicz exteriorization procedure, while the morbidity is much less. Probably it is a little more dangerous for resection of the sigmoid and rectosigmoid, but it surely seems safer for the right and transverse portions of the colon, where a modified Mikulicz procedure has given a

mortality of 16.6 per cent in expert hands. From 24 recent consecutive aseptic end to end anastomoses there were 2 deaths, or a mortality of 8 per cent. One patient with carcinoma of the cecum, a man of 73, died of an intravenous reaction, and the second had renal suppression, hematuria and ileus without leakage or peritonitis. Several of the patients who recovered were over 70, and one was 85. One had a resection of a cancerous stomach and transverse colon with intermediate abscess; 1 had a combined end to end resection of cancerous jejunum and transverse colon, and a third had a resection from the proximal portion of the transverse colon to the sigmoid with a large resection of abdominal wall containing an abscess from a perforated carcinoma of the splenic flexure. Such one stage resections were formerly considered very dangerous, but now, when performed with careful attention to detail, offer a superior result, especially with elderly, debilitated patients, who often cannot withstand prolonged confinement to bed and repeated operations. The loop of cancerous colon, with attached peritoneal folds, mesentery and lymphatics, is liberated. The arms of the loop, wide of malignant tissue, are alined by lateral guy sutures and divided between Payr or short clamps by cautery. This leaves the distal and proximal ends of the colon crushed together in a single clamp, which is turned over. Two or three rows of seroserous sutures are then introduced, the clamp is rotated back to its former position and a continuous Cushing suture is introduced anteriorly over it. As the clamp is partly opened and withdrawn this suture is tightened, inverting and closing the anterior edges of the bowel without leakage. One or two anterior outer rows of interrupted seroserous sutures of 36 B. & S. gage alloy steel wire are inserted, corresponding to those introduced on the posterior side. The fine wire is used universally on peritoneal surfaces, since it does not lead to perintoneal adhesions, as does catgut or silk. Care should be taken to use only viable ends of bowel for the anastomosis, to have the sutured surfaces denuded of all fat and carefully apposed so as to be absolutely gas and water tight and to do an associated complemental appendicostomy or enterostomy. With the Mikulicz operation, as with any colostomy, there are a certain number of deaths from spreading pyoderma and other complications, and often, even when a muscle-splitting incision is used, a weak area is left in the abdominal wall.

The lowest mortalities from resection of the colon in recent years have been reported by operators who have become adept in a single stage operation. In our experience, even when it has been necessary to resect in addition a portion of infiltrated bladder, abdominal wall, ureter, stomach, adjacent intestine or vagina or to remove the uterus and appendages, we have found the single stage operation of advantage. In recent years we have not found it necessary to compromise one of these prolonged, complicated single stage operations on account of the

shock or unfavorable condition, and none of the patients in whom multiple resections for malignant extensions were possible has died of the operation.

A four clamp method facilitates the removal of the ileum, uterus or other organ to which the cancerous colon has become attached. Two light clamps are applied on each side of the bowel lateral to the growth, and the colon is divided by cautery between each pair of clamps. This leaves the diseased intestinal segment attached to the uterus or other organ, which is then removed or resected. The distal and proximal clamps are now apposed over a single Payr clamp and burned off. The end to end aseptic suture is then completed over the single clamp, as previously described (fig. 3).

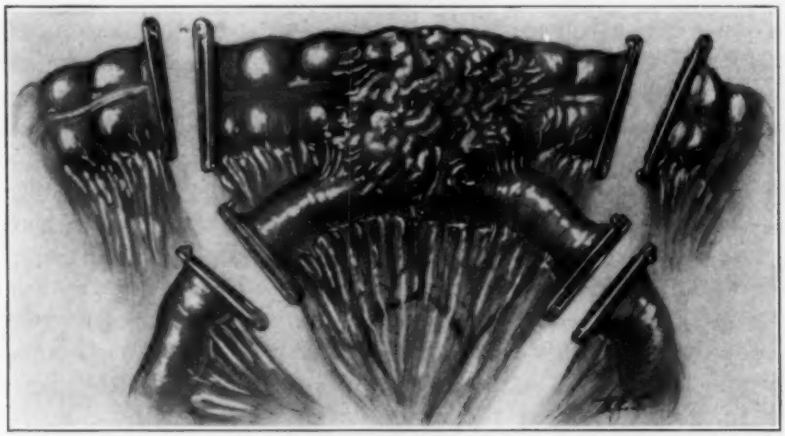

Fig. 3.—Use of eight short clamps as in a combined aseptic resection of colon and jejunum for infiltrating carcinoma or jejunocolic fistula. The clamps have been applied and the segments divided by cautery.

When the cancer has invaded an adjacent loop of small intestine, it usually is feasible to fold the intestinal loop together and then apply two Payr or de Martel clamps obliquely across the base of the loop, which is divided by cautery between the two clamps. A similar operation may be used when a cancer of the transverse colon has invaded the stomach. Again, adhesions or other condition may render an eight clamp double resection desirable. Here the small and the large intestine are resected, each with four clamps, as previously described (fig. 4).

In resections of the colon above the sigmoid, including the ileocecum, for a number of years we have used only end to end anastomoses. By apposing an oblique section of the smaller ileum to a transverse section of colon, a satisfactory end to end union may be made. A side to side anastomosis is a longer and more complicated operation; the blind ends

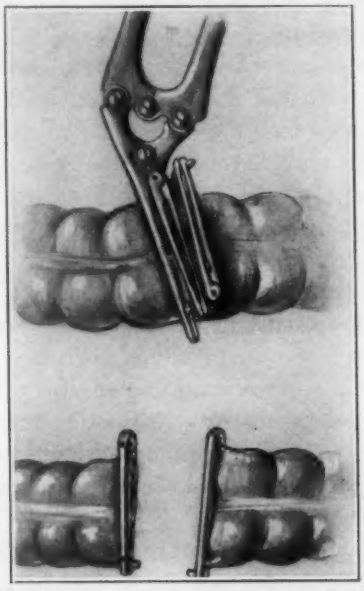

Fig. 4.—Method of end to end anastomosis over a single clamp after the diseased adherent segment shown in figure 3 has been removed. The clamped ends of bowel are alined and clamped together by an underlying Payr clamp, and the ends are burned off by cautery. This leaves the ends of the bowel in the grasp of the single Payr clamp in position for an aseptic end to end suture.

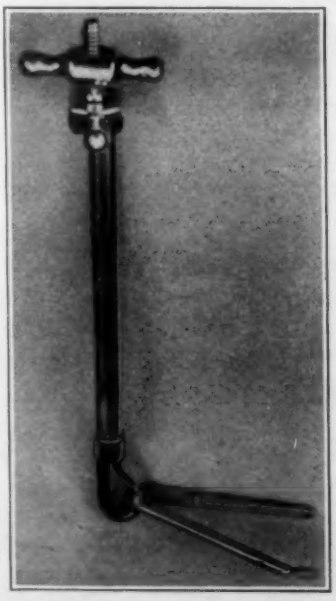

Fig. 5.—Removable clamp holder desirable for manipulation of the short clamps in the depths of the abdomen.

may become distended with fecal material and may even open under reversed peristaltic pressure.

When the cancer has invaded the anterior abdominal wall, this may be resected en bloc with the diseased segment of bowel. Even when the colon has perforated into the abdominal wall with the formation of a localized abscess, the en bloc resection should be used if possible. In 1 case a large carcinoma of the splenic flexure had perforated into the abdominal wall; it had been drained for four months elsewhere and then closed, to recur three months later. Even then it was possible to resect the transverse and the descending colon with a large segment of abdominal wall, enclosing the abscess, and to perform an end to end aseptic anastomosis between the proximal portion of the transverse colon and the sigmoid over a single clamp (fig. 5). Primary union followed, with the exception of a minute and transient sinus. While a complemental enterostomy is less often required after resection of the right side of the colon, it will prove life-saving in certain cases, and at present is our routine practice.

SUMMARY

An experience of over 200 operations for cancer of the lower part of the bowel, performed in one stage without abdominal colostomy, has shown that such operations may be done with a relatively low mortality and with satisfaction to the patients.

In over 85 per cent of the patients a functional anus may be preserved without destroying the radical nature of the operation.

An experience of 12 operations has shown the feasibility of transferring to the perineum an abdominal colostomy opening left by a previous operation.

The transfer of the colostomy fistula has enabled patients to become acceptable for professional and office work, for household duties and for marriage.

Plastic procedures for restoring function to the damaged anal sphincters are described and illustrated.

The Mikulicz procedure often may be supplanted with advantage by a more accurate one stage aseptic anastomotic operation, for which a single clamp method is described. In resections of the abdominal colon, the routine use of suction drainage and complemental enterostomy or appendicostomy and of nonirritating metallic sutures has been found of advantage.

ABSTRACT OF DISCUSSION

DR. LOUIS J. HIRSCHMAN, Detroit: I should like to say a word of commendation for Dr. Babcock and a few others who still feel that some patients suffering from carcinoma of the large bowel have the right to choose where the site of the colostomy may be located, provided that it does not in any way interfere with their ultimate recovery. I happen to be one of a very small group

who still feel that a patient can have a colostomy in the normal site and live just as long as if he had a colostomy on the abdomen, provided that the procedure in each case is well selected.

Those of you who will live longer than I shall will see the time come when more and more perineal colostomies and implantations into the perineal region will be done, and some time I hope that sphincters will again be able to function in persons who have had carcinomas excised.

DR. FRANK H. LAHEY, Boston: One can easily lose sight of certain things, the most important of which is that, given enough experience, a surgeon will select the type of operative procedure with which he has had the greatest success. This applies particularly to where one places the colostomy. Both Dr. Babcock and Dr. Hirschman have had a large experience, and they can select any type of procedure they choose and probably get very good results.

With regard to our own experience, I can only say that my associates and I like the abdominal colostomy. We like it for the reasons that we can even mobilize the splenic flexure and, if we wish, bring it down to the colostomy opening and that we can remove large segments of gland-bearing area and long segments of bowel above the lesion. We have not infrequently had to mobilize the splenic flexure, and we can feel sure that when implanted on the abdominal wall the blood supply of the terminal end of the colostomy opening is adequate and intact. We feel that an opening is more hygienic and easily cared for in the abdominal wall where one can get at it than anywhere in the perineum or posteriorly. Having seen over 1,300 carcinomas of the colon and rectum, with an operability rate of between 80 and 90 per cent, a mortality rate of 10.25 per cent and an average nonrecurrence rate of 50 per cent, we feel that such lesions offer great prospects for a high five year nonrecurrence rate and therefore must be approached as aggressively as possible.

There are certain basic things to remember about a colostomy. So many people are unhappy even to consider the question of colostomy because nearly every one—patients, practitioners and many surgeons—thinks of it only in terms of the palliative colostomy. This, of course, is a proper unhappiness, because everything that is said about a colostomy when it is a palliative one is true. The lack of control of the movements and of the blood and pus is not the result of the colostomy but is largely due to the unremoved lesion.

No matter where one does a colostomy there is no sphincter-like action which produces control. It can never be controlled mechanically. It is controlled dietetically, by teaching a person to constipate himself and by letting the colon have time to habituate itself to the fact that a new segment has taken on the function of the anal reservoir, and also by establishing the fact in the patient's mind that the bowel no longer moves voluntarily but that defecation is accomplished by irrigation every second or third day.

We are very careful not to discharge a patient after colostomy, but to keep in touch with him for six months. If he has colostomy accidents (soiling) it is during the time when these are occurring that he loses his morale and needs reassurance. If he has two or three bad experiences he will be so discouraged that it will be difficult to keep him enthusiastic and interested in his diet and proper handling of his colostomy opening. The patient learns during this time to handle any loose movements with paregoric and that he cannot take liberties with his diet or he will have loose movements which will be distressing to him. He learns that it is necessary to take plenty of time for his irrigation, to take time getting the catheter in—in fact, during this time he learns all the measures for successful management of his colostomy opening.

We have learned, in addition, that in certain persons keloid scars develop about the colostomy fistula and that if they do not insert the third finger, down to the middle knuckle, through the opening every time they irrigate it, it will so contract that it will interfere with the successful removal of feces. None of our patients wears a bag. If a patient learns how to constipate himself and how to handle his colostomy opening, he needs only a piece of gauze and an elastic belt about the abdomen.

I feel certain that if we could disseminate throughout the country the knowledge that a colostomy performed after the lesion is removed is an utterly different problem from a colostomy done as a palliative measure, we should then avoid the frequent fear and objection to a colostomy, hesitation about accepting the operation and unwise and undesirable delay.

Dr. W. Wayne Babcock, Philadelphia: As the functional usefulness of the sphincters after these extensive operations has been questioned, Dr. Bacon and I are here showing in motion pictures a series of patients who after the operation are voluntarily contracting and relaxing the perianal muscles. The pictures demonstrate that the sphincters may still be functional after radical removal of 45 to 65 cm. of bowel. Most of the patients shown have had single stage abdominoperineal resection, and 1 a posterior perineal resection. One had the less desirable keyhole type of opening after a postanal delivery of the sigmoid, which now has been corrected by plastic operation. The anterior perineal withdrawal of the liberated bowel gives the most direct opening through the anus and has the advantage of not dividing the posterior, i. e. the thicker and more important, part of the sphincter muscles. In our series all but 2 of the operations have been performed in a single stage. With modern anesthetic methods, shock is rarely a problem, even in prolonged and complicated intestinal resections.

A very radical removal of rectosigmoid may be done with little perineal evidence of the operation and with retention of a degree of control of gas, good control of solid fecal material and, perhaps at most, leakage only during diarrhea.

An important problem of colostomy, which is lessened by the perineal opening, is the control of offensive gas, which may cause the patient to lose his position.

TRAUMATIC HEMORRHAGE OF THE INTERNAL CAPSULE

ALFRED ANGRIST, M.D.
AND
NATHAN MITCHELL, M.D.
JAMAICA, LONG ISLAND, N. Y.

The existence of traumatic intracerebral hemorrhage is generally conceded, yet the finding of a blood clot in the region of the internal capsule at autopsy is ordinarily accepted as positive evidence that the lesion represents a spontaneous hemorrhage. If signs of trauma are present, the temptation is to consider such trauma as secondary to the unconsciousness and fall resulting from the apoplexy.

Courville and Blomquist,[1] in a discussion of traumatic intracranial hemorrhage, presented 38 instances occurring among 439 cases of fatal craniocerebral injuries. Only 7 cases of traumatic hemorrhage into the ganglionic region (external capsule and lenticular nucleus) were included. They stated:

> . . . . No example of gross hemorrhage into the posterior limb of the internal capsule, such as appears spontaneously in cases of hypertension or arteriosclerosis, has been observed by us. It may, therefore, be safely assumed that gross hemorrhage in this region is not the result of trauma, for, of all portions of the brain presenting evidences of injury, this particular region seems to be most notably free.

Jelsma[2] urged that traumatic hemorrhages be not "confused with apoplectiform lesions which are found in the internal capsule and deeper in the brain, though the traumatic clot may be as deeply placed as one in apoplexy." There have been numerous clinical descriptions of traumatic intracranial hemorrhage with involvement of internal capsule inferred by the existence of hemiparesis. Inasmuch as nearly all such cases represent recoveries after surgical evacuation of the clot or lack confirmation by autopsy, the evidence is indirect. Most such cases present the picture of *Spätapoplexie* of Bollinger with a time interval varying from days to months or even years. Only 1 instance of a traumatic fresh hemorrhage of the internal capsule at autopsy was found

From the Department of Pathology, Queens General Hospital.

1. Courville, C. B., and Blomquist, O. A.: Traumatic Intracranial Hemorrhage, with Particular Reference to Its Pathogenesis and Its Relation to "Delayed Traumatic Apoplexy," Arch. Surg. **41**:1 (July) 1940.

2. Jelsma, F.: Common Traumatic Lesions, Kentucky M. J. **34**:264, 1936.

in the literature; this was described by Berner.[3] Several late effects of hemorrhage of the internal capsule ostensibly caused by trauma have been described, including an old lesion in the genu of the internal capsule eighteen years after the injury, described by Spiller.[4]

In this presentation we wish to offer 7 instances of verified traumatic hemorrhage of the internal capsule and to discuss the medicolegal significance of such lesions. Hemorrhage into the internal capsule occurring immediately at the time of injury is admittedly rare, having occurred in only 7 instances in approximately 320 cases of trauma of the head in which autopsy was done. The cases reported here all represent instances of established trauma with varying-sized hemorrhages in the internal capsule. In some, the hemorrhage was limited to the region of the internal capsule without other marked cerebral lesions and without fracture of the skull. In others extensive associated morphologic evidence of trauma was noted in the skull and in the brain. In all the internal capsule lesion bore no relation to any superficial brain laceration, contusion or source of bleeding. The hemorrhages truly represented independent deeply placed parenchymal foci of bleeding within the cerebrum. Hemorrhage into the adjacent basal ganglions was also present in several of them. All cases with hemorrhage into the basal ganglions as well as all other deeply placed hemorrhages without involvement of the internal capsule have been eliminated. The lesions described herein corresponded to the first type in the classification of traumatic hemorrhages by Bailey[5] and represented hemorrhages "which occur at the moment of injury."

REPORT OF CASES

Case 1.—N. B., a 49 year old man, was found in coma at the foot of a subway stairway. A hematoma was noted over the left occipitoparietal area. Deep irregular breathing with bubbling rales and diminished reflexes were present. The spinal fluid was bloody. Death occurred within two hours. At autopsy multiple skull fractures were found in all fossae. Extensive contusion of the surface of the right frontal, parietal and temporal lobes was present, with adjacent petechial hemorrhages. On horizontal section, a hemorrhage 3 by 2 cm. was seen in the anterior limb of the left internal capsule (fig. 1 *A*), and a hemorrhage of similar size and shape was found beyond the genu at a deeper level in the posterior limb of the internal capsule (fig. 1 *B*). Smaller deeply placed petechial hemorrhages were noted in the head of the right caudate nucleus, the splenium of the corpus callosum, the pons and the floor of the fourth ventricle. The kidneys were natural, and the heart showed only limited hypertrophy. The clue to the cause of the fall in this instance was found in the recovery of 3 plus alcohol, equivalent to 15 cc. per hundred grams, from the brain and the liver. The alcoholism and the multiplicity and the severity of the traumatic lesions would tend to rule out coincidental spontaneous apoplexy.

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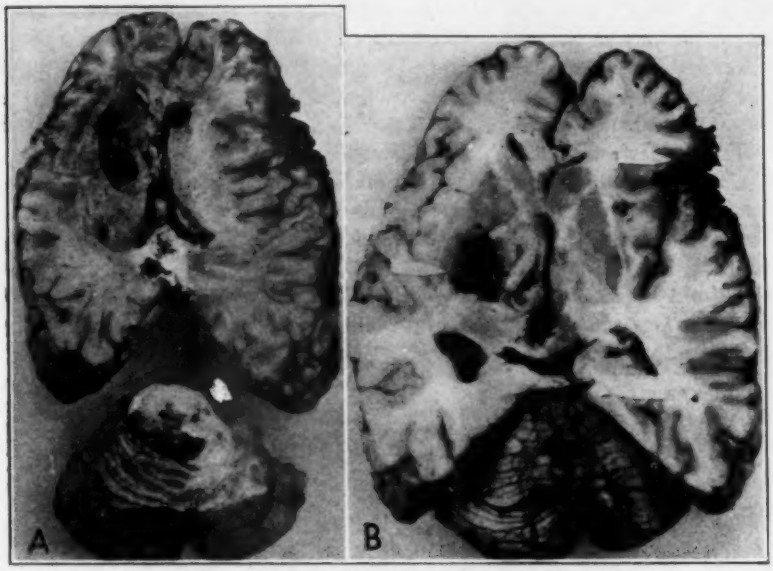

Fig. 1 (case 1).—*A*, section of the cerebrum and the brain stem showing hemorrhage in the anterior limb and the genu of the left internal capsule and the upper portion of the pons and the floor of the fourth ventricle. Note hemorrhage in the splenium of the corpus callosum. *B*, horizontal section of the cerebrum at the lower level showing hemorrhage in the posterior limb of the left internal capsule. Note surface laceration of the right frontal and temporal lobes.

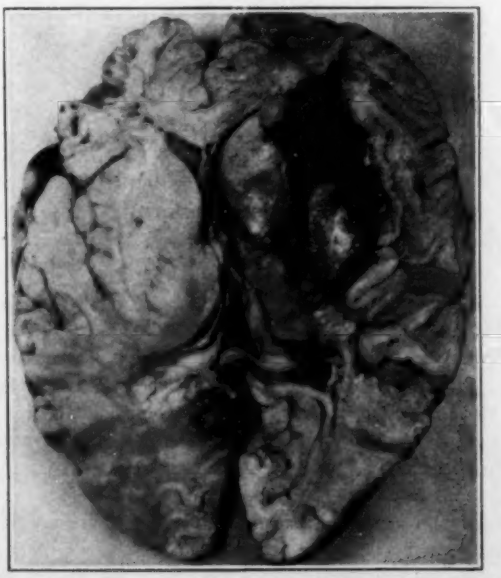

Fig. 2 (case 2).—Section showing massive hemorrhage involving all but the most posterior portion of the right internal capsule, the lenticular nucleus and the adjacent subcortical white matter. Note distortion of the right lateral ventricle.

Case 2.—G. C., a 31 year old man, was struck by a passing automobile while changing the tire on his car. He was brought to the hospital in coma and died shortly afterward. At autopsy external evidence of injury was found in the form of multiple abrasions and contusions of the face and the right and left frontal regions. Comminuted fracture of the nose was present, but careful examination of the skull revealed no other fracture. A small amount of subdural and subarachnoid hemorrhage was seen bilaterally. Horizontal section of the brain (fig. 2) showed a massive area of hemorrhage involving the right internal capsule, the lenticular nucleus and the regional gray and white matter extending as far laterally as the island of Reil. This area measured 4 by 7 cm. and extended to within 3 and 4 cm. of the surface cortex. No surface lacerations of the brain were found. A moderate amount of punctate hemorrhage was seen in the left frontal and right frontoparietal regions at the very junctions of gray and white matter.

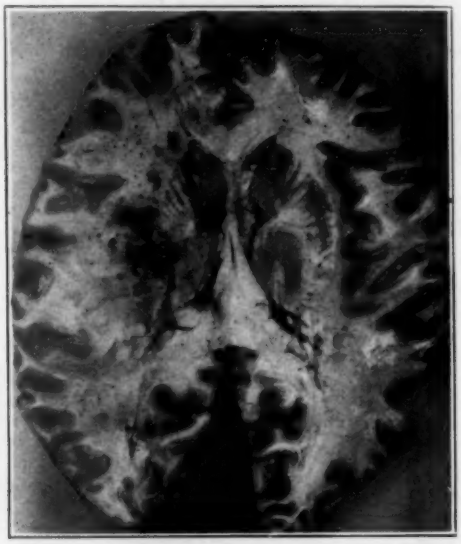

Fig. 3 (case 3).—Section showing level above the main blood clot with multiple varying-sized discrete and confluent hemorrhages in the left internal capsule and the medial portion of the putamen.

Case 3.—W. M., a 4 year old boy, fell from a ladder while playing with some friends and landed on his head. He died almost immediately. At autopsy extensive fractures of the vertex and the base of the skull were seen. There was separation of the frontoparietal suture on the right with a depressed fracture 1 by ½ in. (2.5 by 1.3 cm.) in the right frontoparietal region. On the left a linear fracture extended along the parietal bone. Both fractures were traced around to the base in the region of the sella turcica with complete separation of the anterior and posterior parts of the skull. Despite the extensive injury to the skull, the brain appeared normal externally. On horizontal section, an area of hemorrhage was observed in the left internal capsule which extended into the adjacent basal ganglions, particularly the lenticular nucleus. Figure 3 represents a photograph of the lesion at a level above the main blood clot. The area of

bleeding represented confluence of many small areas of hemorrhage. Although some petechiae were noted in the adjacent white matter, no other areas of hemorrhage were noted in the brain.

CASE 4.—N. J., an 8 year old boy, was struck by an automobile and died eight hours later without regaining consciousness. Abrasions but no lacerations were found about the face and the head. Autopsy revealed extensive basilar skull fracture with only limited surface lacerations in the frontal and right parietal regions. A horizontal section of the cerebrum revealed extensive focal hemorrhages in the white matter of the frontal lobes and the corpus callosum. There were numerous streaked hemorrhages throughout the entire length of the internal capsule on the left side, and a larger area of hemorrhage 1 cm. in diameter extended laterally from the internal capsule into the adjacent basal ganglions (fig. 4). A small hemorrhage was noted in the posterior limb of the right internal

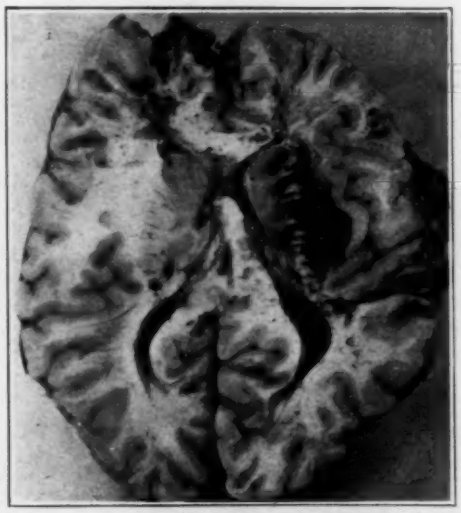

Fig. 4 (case 4).—Section showing multiple streaked hemorrhages in the left internal capsule and the adjacent putamen. Note extensive contusion and laceration of the left temporal and right frontal lobes. Note small hemorrhage in the posterior limb of the right internal capsule and numerous varying-sized concussion hemorrhages in subcortical white matter.

capsule. Dissection revealed no surface laceration or hemorrhage continuous with the lesion in the internal capsule.

CASE 5.—J. K., a 38 year old policeman, was thrown from his motorcycle while traveling at a considerable rate of speed. He was brought to the hospital in a comátose condition. He showed lacerations of both eyebrows with regional hematoma and ecchymosis of both orbits. Overactive knee jerks and bilateral ankle clonus were noted. He remained in coma, his temperature rising to 106 F. on the fourth hospital day with death occurring soon after. Autopsy revealed grouped focal hemorrhages involving the right internal capsule and the lenticular nucleus. Some of the hemorrhages measured more than 1 cm. in diameter and merged with adjacent hemorrages of similar size. At a deeper level isolated

smaller focal hemorrhages were found in both anterior and posterior limbs of the internal capsule. A few streaked hemorrhages were seen in the subcortical white matter in the region of the frontal and parietal lobes on the same side. No skull fracture was present.

CASE 6.—P. D., a 45 year old white woman, was injured in an automobile accident and was brought to the hospital in an unconscious state and in shock. There was laceration of the chin and contusion of the face just above the forehead; large laceration of the scalp was also present. There were comminuted fractures of the tibia and the fibula. The left pupil was larger than the right, and both reacted. She improved for a few hours and then became restless, went into deep coma and died two days later. At autopsy the brain revealed grouped

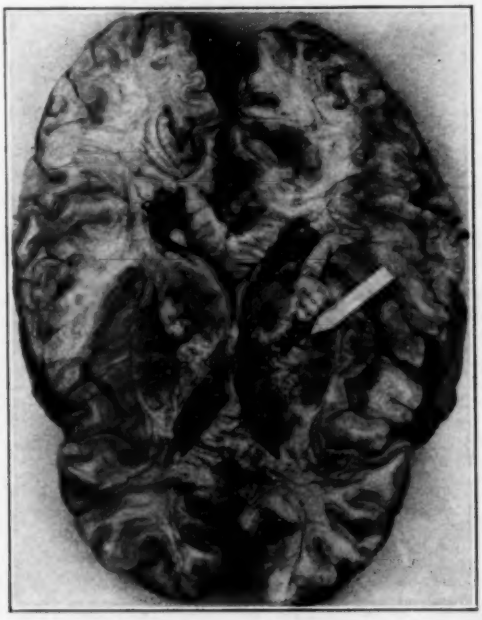

Fig. 5 (case 6).—Section showing grouped small hemorrhages in the posterior limb and the genu of the right internal capsule. Some of the blood clot has been displaced.

small focal areas of hemorrhage in the region of the genu extending backward for approximately half of the posterior limb of the right internal capsule (fig. 5). A smaller zone of softening or hemorrhage was noted in the corresponding area of the other internal capsule. A single small hemorrhage was also found in the left lateral wall of the fourth ventricle. No skull fracture was seen, and no bleeding into the ventricular system or in relation to the cerebral meninges was found. The immediate cause of death was extensive bronchopneumonia.

CASE 7.—J. B., a 28 year old jockey, was thrown from his horse during a race, became unconscious immediately and showed laceration of the right side of the head with hematoma of the temple. He was incontinent, and decerebrate spasm developed. The jaws were fixed. Reflexes on the right were hyper-

active, but the right arm and leg were flaccid. The left arm and leg were spastic. Abdominal reflexes were absent. A right-sided ankle clonus was present, and the knee jerk was hyperactive on the right. Bilateral Babinski reflexes were noted. Roentgen examination of the skull failed to reveal any fracture. The frequency of the decerebrate spells lessened for a while, but the right-sided paresis persisted. The right pupil was three times larger than the left and failed to react to light. The spinal fluid was bloody. Hyperpyrexial signs of pneumonia developed, and death occurred six days after admission. Clinical diagnosis by Dr. Richard Grimes was contusion and laceration of the left temporal lobe and traumatic left intracerebral hemorrhage. At autopsy extensive hemorrhage was found low down in the posterior limb of the internal capsule just above the cerebral peduncle on the left side extending into the lateral portion of the adjacent thalamus. Some small areas of hemorrhage were noted elsewhere in the basal ganglions in the thalamus in the internal capsule, in the cerebrum and in the cerebellum. No skull fracture was found.

Fig. 6 (case 7).—Coronal section of the inferior portion of the cerebral hemispheres showing large area of hemorrhage in the posterior limb of the internal capsule just above the cerebral peduncle on the left side. Note involvement of the lateral portion of the thalamus and the subcortical white matter.

COMMENT

The differentiation of spontaneous intracerebral hemorrhage from the variety of intracerebral hemorrhage due to trauma ordinarily presents no difficulty. The so-called spontaneous medical hemorrhage, or apoplexy, is centrally placed in the cerebrum with evidence of external trauma in the form of injury to the scalp, the skull and the surface of the brain, ordinarily only minimal. The history usually rules out any causative trauma and establishes the sequence of events. Spontaneous hemorrhage is naturally associated with local vascular disease. It is more common in the older age group and often occurs under circumstances under which contributory trauma is impossible. Generalized vascular disease, hypertension, local atheroma, sclerosis and syphilis often will be found in the spontaneous variety of hemorrhage.

There are no trustworthy gross pathognomonic features of spontaneous hemorrhage to differentiate it from the traumatic variety. The adjacent tissue does usually show more widespread distribution of small petechiae in the nontraumatic lesions. The zone of softening is also usually wider. There is usually a gradation in size and number of the petechiae about the zone of spontaneous hemorrhage. There exists a greater tendency to respect and preserve the natural landmarks of the brain, no doubt dependent on the individuality of blood supply. Multiple foci of bleeding are less common in apoplexy. We have seen, however, numerous instances of blowout hemorrhages in the pons when a spontaneous hemorrhage extended into the ventricular system without any associated trauma. In general spontaneous hemorrhage is placed in the region of the geometric center of the corresponding mass of brain tissue. In the cerebrum this does correspond approximately to the region of the internal capsule and adjacent basal ganglions, and the lenticulostriate vessels are usually implicated as the main source in this location.

In contrast traumatic intracerebral hemorrhages are usually associated with considerable evidence of external trauma in the form of contusion and laceration of the brain surface or by scalp and/or skull injury. In 4 of the cases in the group presented here there was extensive injury. It is of pointed interest, however, to call attention to the fact that no fracture of the vault or the base was present in 4 of the 7 cases. Evidence of injury to the surface of the cerebral cortex was entirely lacking in case 3 even though an extensive fracture of the skull was present. The age incidence in the present group of traumatic hemorrhages is impressive. Four patients were under 40 with 1 child 4 years old and another 8 years of age. The youth of these patients rules out consideration of basic vascular disease, such as is found in older persons. All circumstances favor dissociation from vascular disease. Subdural or epidural hemorrhages are common following trauma, but subarachnoid hemorrhages may be associated with both trauma and nontraumatic lesions. In general hemorrhages due to trauma tend to be multiple and are placed in the external aspect of the brain. We do not agree with Bailey that in all cases of traumatic intracerebral hemorrhages some previous disease process exists in the vessels. The cerebral vessels will more often be found natural in cases of traumatic hemorrhages, whether superficial or deep.

There are two types of traumatic intracerebral hemorrhage. One form is superficially placed and represents a gyrus distended by blood clot. This usually results from venous bleeding. This blood clot takes an interval of time to appear, and it is this form of intracerebral hemorrhage which constitutes the more common basis for *Spätapoplexie*. This particular form of traumatic hemorrhage is of considerable clinical

importance and has received a great deal of surgical study recently. This expanding blood clot may be looked on as a variant of the ordinary subdural hemorrhage, and the clinical pictures approach each other. Such traumatic hemorrhages are found usually in the region of a surface contusion and laceration. This form of hemorrhage can reach considerable size and act like any expanding lesion. Numerous instances of identification by clinical means, with and without the aid of encephalography, with subsequent recovery for the patient are found in the literature. They all have in common the feature of extending to the surface of the brain usually at the focus of origin.

Another form of traumatic hemorrhage is the so-called concussion or blowout hemorrhage with no connection with any surface lesion of the brain. This form particularly comes well within the scope of our present study. The pons is the favorite site for such lesions. These may be found throughout the brain. They are seen more often in the white matter of the cerebrum and in the gray matter of the spinal cord. In the pons they have a characteristic streaked appearance, undoubtedly caused by the orientation of fiber tracts. A similar streaked appearance is noted in the region of the internal capsule in figure 4. Other than their location in the pons there seems to exist no particular preferential site.

Courville and Blomquist have analyzed the relation of the direction of force in injury to the location of the hemorrhages within the brain. They favor the impact of the force in the temporal region for deeply placed ganglionic hemorrhages. In only 1 of our cases was there external evidence of trauma in the lateral temporal region. In 4 of the cases the force of injury was apparently applied to the region of the face. In the other 2 there was scalp injury in the region of the vertex or the occipitoparietal areas. We have seen a wide range of gradation in size and form of such traumatic concussion or blowout hemorrhages. They vary in different cases of trauma and in the same case. Microscopic hemorrhages and petechiae may be associated with larger varying-sized blood clots. The multiplicity of such lesions helps establish their traumatic nature readily. When, however, a single large concussion or blowout hemorrhage is found centrally placed, particularly in the internal capsule, and the history of trauma is equivocal in an older person with hypertension, the lesion may readily be interpreted as spontaneous apoplexy. It follows that any evidence of trauma present will be misinterpreted as secondary and as precipitated by the hemorrhage.

The following case of spontaneous bleeding represents a single instance that is chosen because of the excellence of contrast to case 1 in the series already presented. From the standpoint of circumstantial evidence, both persons were found at the bottom of a stairway in coma. Both showed hemorrhage into the internal capsule, yet the lesion of one

was traumatic in origin (case 1), the person having fallen because of his inebriation; and the other was obviously spontaneous (case 8) with the fall and the injury precipitated by spontaneous hemorrhage in the internal capsule caused by underlying vascular disease.

Case 8.—An 82 year old man was admitted in coma, having been found at the foot of the cellar steps. He showed a hematoma in the left temporal region. The pupils were pinpoint and fixed. Spinal tap showed no increase in pressure. There were 100 cells per cubic millimeter with lymphocytes predominating and only a few red blood cells. Generalized convulsions appeared, and the patient required amytal. Muscle rigidity was absent on admission but appeared on the third day. The temperature rose to 102.4 F. with the pulse becoming imperceptible and respiration ceasing shortly after. There was no return of consciousness during the entire stay in the hospital. At autopsy the brain showed a deeply

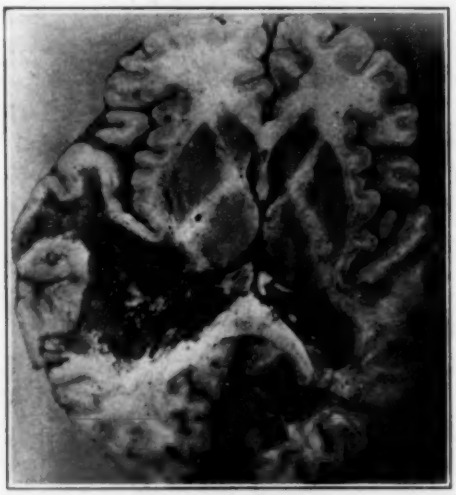

Fig. 7 (case 8).—Section showing massive spontaneous hemorrhage into the posterior limb of the internal capsule with involvement of the regional white matter of the parietal and occipital lobes. Note blood clot in ventricle.

placed massive left internal capsular hemorrhage with involvement of the optic radiation and regional white matter of the parietal lobe. Extension to the ventricular system was present. Some surface lesions were found in the left frontoparietal region but were of a limited nature. The kidney showed rather severe nephrosclerosis, and the heart showed marked hypertrophy with prominent involvement of the left ventricle.

In none of the cases in which there was a history of trauma was there evident disease of the cerebral vessels. The initial hemorrhage was undoubtedly due to the direct trauma. The presentation of the 7 cases of traumatic hemorrhage into the internal capsule should call attention to the possibility that lesions in this region, ordinarily accepted as the focus for spontaneous hemorrhage only, may occur as the result

of trauma. In the present day, when trauma plays such an important role in our routine lives, this realization is of importance to avoid occasional dislocation of justice. In all the cases represented hemorrhage with trauma was the obvious mechanism, yet the findings simulated those of spontaneous apoplexy. Variations from petechiae to bulky blood clots are represented. It should be stressed that such hemorrhages may occur with and without the skull fracture. Courville and Blomquist have discussed the location of this form of hemorrhage throughout the brain and in the basal ganglions limited to the lenticular nucleus and the external capsule. No group of cases of traumatic hemorrhages localized in the internal capsule at autopsy has been found in the literature.

Discussion of the mechanism involved in the concept of such blowout hemorrhages is being reserved for a future presentation, with the inclusion of some experimental data. The causation of concussion or blowout hemorrhages, of which the cases presented are merely larger variants, has been studied by numerous authors.[6] Let it suffice here to state that concussion or blowout hemorrhages are identical in the internal capsule, whether small or large, with the ordinary concussion or blowout hemorrhages seen so often in the pons or elsewhere in the white matter in cases of trauma of the brain. We do not wish to enter into the controversy as to the relation of such focal and petechial hemorrhages to the syndrome of concussion. We merely wish to imply that in some cases of head trauma such multiple focal hemorrhages occur. This does not deny the existence of the syndrome of concussion without the existence of such hemorrhagic lesions. For this purpose the descriptive term blowout hemorrhages is distinctly preferable.

Whether smaller focal areas of hemorrhage of this sort might be the site of subsequent spontaneous apoplexy is an open question. The accepted propensity of massive hemorrhage to occur in focal areas of

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old softening or hemorrhage does give significance to traumatic lesions of the internal capsule too small to contribute to the symptom picture at the time of injury. A theoretic basis is thus offered for the delayed contribution by trauma to the causation of a second and much rarer form of *Spätapoplexie*. Injuries without immediate major evidence of bleeding into the internal capsule thus can be of some importance. It must be emphasized that although this form of *Spätapoplexie* seems to be frequently discussed in the literature it is distinctly rare in our own experience. It is as yet based on little demonstrative evidence and lacks full confirmation.

CONCLUSIONS

Traumatic hemorrhages of considerable size can involve the internal capsule. Seven cases are presented.

Such hemorrhages may be confused with spontaneous cerebral hemorrhage on the basis of their location.

The history, circumstances of injury, analysis of associated brain and skull trauma and basic vascular and other lesions established by a complete autopsy procedure are essential for the proper analysis and understanding of hemorrhages occurring in this location as elsewhere in the brain surface.

It is suggested that such hemorrhages are variations of the ordinary concussion or blowout hemorrhages with an identical causal mechanism.

Dr. Richard Grimes, Assistant Medical Examiner, allowed us to study much of the material used in this paper.

82-68 One Hundred and Sixty-Fourth Street.

TOTAL CIRCULATING PLASMA PROTEINS IN SURGICAL PATIENTS WITH DEHYDRATION AND MALNUTRITION

INDICATIONS FOR INTRAVENOUS ALIMENTATION WITH AMINO ACIDS

WILLIAM E. ABBOTT, M.D.
CLEVELAND
AND
ROBERT C. MELLORS, PH.D.
BALTIMORE

In recent years a great deal of emphasis has been placed on the preoperative and the postoperative care of surgical patients [1] with the hope of further reducing the mortality rate. With such a major surgical procedure as gastric resection, pulmonary complications (atelectasis, pulmonary edema and bronchopneumonia) play an important role. With the improvements in operative technic and anesthesia these conditions now account for a large percentage of the postoperative complications that still exist. With the advent of the use of sulfonamide compounds the mortality rate will probably be further reduced, but it has always been the hope that pulmonary complications could be prevented and that the added risk to the patient and the need for treatment could therefore be eliminated.

The removal of mucus by intratracheal aspiration,[2] hyperventilation of the lungs [3] and careful application of adhesive tape and abdominal binders [4] to prevent restriction of the thoracic cage have all contributed to more efficient postoperative care. It is believed, moreover, that by employment of gastric suction ileus may be avoided and thus the diaphragm will have more freedom of motion and aerate the lungs more

This study was aided by a grant from the John and Mary R. Markle Foundation.

From the Departments of Surgery and Biochemistry, Western Reserve University School of Medicine.

1. Pack, G. T., and Scharnagel, I. M.: The Preoperative and Postoperative Care of Patients with Gastric Cancer, Am. J. Surg. **45**:435-451, 1939. Robillard, G. L., and Shapiro, A. L.: Preparation for Operation and Postoperative Care of the Patient with Cancer, Arch. Surg. **44**:840-880 (May) 1942.

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efficiently. Furthermore, it has been stated that the type of anesthesia employed (inhalation, spinal or local) apparently does not alter the incidence of pulmonary complications appreciably but that the duration of the anesthesia is of considerable importance.[5]

Nutritional disorders have been carefully studied, and it has been generally accepted that pulmonary complications occur more frequently in elderly malnourished patients than in others.[6] At the University Hospitals of Cleveland it was found that the mortality rate associated with gastric resection fairly well paralleled the magnitude of the loss of weight in patients with chronic peptic ulcer.[7] It was noted also that patients who showed moderate anemia on admission to the hospital and were given 1,000 to 2,000 cc. of whole blood prior to operation often did much better than patients who had normal blood values on admission and did not receive transfusions because it was assumed that they were not necessary. Hence, this has led us to believe that often a decrease in the plasma volume associated with chronic dehydration masks anemia and hypoproteinemia. In further support of this it was observed that in many instances patients who were admitted because of a gastric lesion had hematocrit values and protein concentrations near normal on admission but had profound drops in these levels after operation without evidence of bleeding, apparently due to hemodilution.

In a recent publication by Walters, Gray and Priestley [6] on carcinoma of the stomach it was stated that malnutrition may be severe and a negative nitrogen balance may exist in such cases but that the depletion of the plasma protein does not often reach levels which are clinically important. Furthermore, it was stated that the degree of anemia more or less indicates the duration of the tumor.

This study was undertaken to demonstrate in an unselected group of patients with carcinoma of the gastrointestinal tract or pyloric stenosis due to ulcer (1) that a protein-deficient state may exist and the plasma protein concentration may be an unreliable index of the extent of the deficiency and (2) that in addition to acute dehydration (primarily due to vomiting) chronic dehydration (principally due to a prolonged inadequate fluid intake) may occur and that the hematocrit value, the plasma protein concentration, the hemoglobin content and the plasma chloride level may not be of value in estimating the magnitude of this prolonged loss of body water.

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5. Judd, E. P.: Early Postoperative Complications in Four Hundred and Fifty Consecutive Inguinal Herniorrhaphies, Bull. Nat. A. Nurse Anesthetists **5**:250-252, 1937. Eliason and McLaughlin.[4]

6. Walters, W.; Gray, H. K., and Priestley, J. T.: Carcinoma and Other Malignant Lesions of the Stomach, Philadelphia, W. B. Saunders Company, 1942.

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METHODS

The plasma volume was measured by the Evans' blue dye (T-1824)[8] method as described by Gregersen and Stewart[9] and modified by Gibson and Evelyn[10] for the photoelectric colorimeter. The expected normal plasma volume was calculated from the body surface area,[11] and it may be stated that since these patients had lost from 10 to 50 pounds (4.5 to 22.7 Kg.) of weight such estimated values would err on the side of being too low.[12] The hematocrit value was determined in duplicate on heparinized blood without dilution by employing Van Allen cell volume tubes,[13] and the plasma protein concentration was for the most part obtained by the micro-Kjeldahl technic. Occasionally the falling drop method as described by Barbour and Hamilton[14] was employed. The value for total circulating plasma proteins was calculated by multiplying the plasma volume in cubic centimeters by the protein concentration per cubic centimeter. A plasma protein concentration of 7 Gm. per hundred cubic centimeters was considered as an arbitrary normal value, and by multiplying that figure by the expected plasma volume and dividing by 100, the expected normal value for total circulating plasma proteins was determined.

RESULTS

The findings are recorded in table 1. In each instance (except for patients 4 and 9) there was a diminished plasma volume. Patients 4 and 9 had moderate anemia on admission to the hospital and received between 1,200 and 2,200 cc. of blood prior to the time our studies were performed. Both of these patients underwent strenuous surgical procedures and had uneventful convalescences.

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8. Supplied by the Warner Institute for Therapeutic Research, New York.

9. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determinations of Plasma Volume with T-1824 and "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142-152, 1939.

10. Gibson, J. G., and Evelyn, K.: Clinical Studies of the Blood Volume: IV. Adaptation of the Methods to the Photoelectric Microcolorimeter, J. Clin. Investigation **17**:153-158, 1938.

11. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Clinical Application of Method Employing Azo Dye "Evans Blue" and Spectrophotometer, J. Clin. Investigation **16**:301-316, 1937.

12. For example, the expected normal plasma volume for patient 8 (table 1), calculated on the basis of weight (57 Kg.) and height (166 cm.) at the time of the study, was 2,600 cc. Prior to his illness the patient weighed 75 Kg., and with the height unchanged the estimated plasma volume was 2,950 cc. Thus the observed plasma volume (2,140 cc.) would be 73 per cent rather than 82 per cent of normal. In addition, the expected normal value for total circulating plasma proteins would be 206 instead of 183 Gm.

13. Van Allen, C. M.: An Hematocrit Method, abstracted, J. A. M. A. **84**: 202-203 (Jan. 17) 1925.

14. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity: Clinical Applications, J. A. M. A. **88**:91-94 (Jan. 8) 1927.

Patient 1 was a man who appeared in moderately good condition on admission to the hospital but gave a history of a loss of 20 pounds (9 Kg.) in weight, occasional episodes of nausea and vomiting and anorexia for three and one-half months. His plasma chloride level was 102 milliequivalents per liter at the time our studies were done. His plasma volume was 66 per cent of his expected normal volume, and although the protein concentration (6.40 Gm. per hundred cubic centimeters) appeared to be near the normal range, the value for total

TABLE 1.—*Values for Plasma Volume and Total Circulating Plasma Proteins of Surgical Patients with Malnutrition*

Patient	Diagnosis	Measured Plasma Volume, Cc.	Expected Plasma Volume, Cc.*	Plasma Volume, Percentage of Normal	Hematocrit Value	Plasma Protein Concentration, Gm. per 100 Cc.	Plasma Protein Concentration, Percentage of Normal	Total Circulating Plasma Proteins, Gm.	Expected Total Circulating Plasma Proteins, Gm.	Total Circulating Plasma Protein, Percentage of Normal
1	Carcinoma of stomach	1,640	2,500	66	47	6.40	91	105	175	60
2	Carcinoma of stomach	1,990	2,690	74	38	5.85	84	116	188	62
3	Carcinoma of stomach with extension to esophagus	1,870	2,900	64	41	5.46	78	102	206	50
4	Carcinoma of stomach	2,900	2,950	98	44	6.65	95	193	206	94
5	Carcinoma of stomach	2,100	2,710	77	44	6.46	92	136	190	72
6	Pyloric stenosis due to ulcer	1,480	2,040	73	37	6.15	88	91	143	64
7	Pyloric stenosis due to ulcer	2,600	2,760	94	40	5.44	78	142	193	73
8	Pyloric stenosis due to ulcer	2,140	2,600	82	40	5.92	85	127	183	69
9	Carcinoma of sigmoid flexure with obstruction	2,030	2,370	86	37	6.22	89	127	166	77
10	Carcinoma of transverse colon	3,700	3,040	122	42	7.46	107	276	213	129
11	Malnutrition; hemorrhage into large ovarian cyst	2,490	2,780	90	42	6.48	93	161	195	83
12	Carcinoma of pancreas; malnutrition; edema	2,330	2,770	84	33	5.06	72	118	194	61
13	Malnutrition; edema	2,660	2,830	94	42	5.30	76	141	198	71
14	Carcinoma of stomach	2,350	2,460	95	43	6.03	86	142	172	83

* Calculated from body surface area.

circulating proteins was 60 per cent of the expected normal. It is likely that most of the dehydration was a result of a prolonged diminished intake rather than of an extensive loss of fluids by vomiting. If it is assumed that the observed plasma volume could be restored to the expected volume by the addition of physiologic solution of sodium chloride and the total circulating proteins remain at 105 Gm., the protein concentration would then fall to 4.20 Gm. (105.0/25). A comparable situation apparently occurred in patients 6 and 7 postoperatively, largely because of the injudicious use of physiologic solution of sodium chloride. In patient 6 by the fourth postoperative day the plasma protein concentration was 4.64 Gm. per hundred cubic centimeters, and generalized

edema was present. The intake of sodium chloride was restricted, and mercupurin and two transfusions of plasma were given. The edema disappeared, and the protein concentration returned to a normal level. This patient had a plasma chloride level of 89 milliequivalents per liter shortly after admission to the hospital. While physiologic solution of sodium chloride was indicated for the hydration of this patient and the plasma protein concentration (6.15 Gm. per hundred cubic centimeters) was well above the so-called edema level, a restoration of the plasma volume to the expected normal in the presence of an amount of total circulating proteins 64 per cent of normal would result in a precipitous fall in the plasma protein concentration to 4.45 Gm. per hundred cubic centimeters ($91 \times 100/2{,}040$).

Patient 7 was moderately dehydrated on admission to the hospital, largely because of inadequate intake of food and water and occasional vomiting. At this time the hematocrit value was 46 and the plasma protein concentration 6.95 Gm. per hundred cubic centimeters. The patient was given 3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride intravenously for three days, and our studies were then made the night prior to operation. The plasma volume had apparently been restored to near normal by the administration of water and electrolytes, but at the same time the hematocrit value and the plasma protein concentration were lower because of dilution. The patient was operated on the next day and given 400 cc. of plasma and 3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride. On the morning of the first postoperative day he was given 2,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride. By noon he had a plasma protein concentration of 5 Gm. per hundred cubic centimeters. Fairly profuse pulmonary edema also had developed, and later atelectasis and bronchopneumonia. At this time it was thought advisable to give a transfusion of blood or plasma and to discontinue the administration of physiologic solution of sodium chloride until the protein level was restored. The patient eventually recovered, but it seems likely that the pulmonary complications might have been avoided. Studies were repeated one month after the operation. At this time the plasma volume had risen to 2,920 cc. and the protein concentration to 6.78 Gm. per hundred cubic centimeters. The amount of total circulating plasma proteins (198 Gm.) compared favorably with the expected normal, which had been calculated prior to the operation.

Patient 8 had total circulating proteins similar in per cent of normal to those of patient 7. This patient was given more plasma and whole blood than the preceding patient, and physiologic solution of sodium chloride was restricted to 900 to 1,000 cc. daily during the immediate postoperative period. The temperature showed only a slight elevation and then returned to normal while the patient was going through an entirely uncomplicated convalescence.

Patient 12 is of interest from the standpoint of therapy. He was a 60 year old man admitted to the hospital because of jaundice. At operation he was found to have carcinoma of the head of the pancreas, and therefore cholecystogastrostomy was performed. Postoperatively his convalescence was complicated by pneumonia and disruption of the wound. He had lost 15 pounds (7 Kg.) prior to his admission to the hospital and because of the prolonged convalescence had continued to lose weight. The patient was seen by us approximately two months after the operation, and studies of plasma volume were made (table 1). At this time he had generalized nutritional edema which had failed to respond to diuretics and transfusions of plasma. He took in a meager diet orally and was in negative nitrogen balance (5 to 8 Gm. daily). Since this patient was metabolizing 40 to 60 Gm. of his own body proteins daily, it was thought that he should have an intake of 60 to 75 Gm. of protein a day plus adequate calories. He was therefore given intravenously 15 per cent amino acids [15] mixed with 10 per cent dextrose. In three days he was free of edema, although his plasma protein concentration had fallen to 4.70 Gm. per hundred cubic centimeters, apparently owing to dilution. The patient was given 60 Gm. of amino acids and 200 to 300 Gm. of dextrose intravenously for ten of the next twelve days.

During this time his entire caloric intake was derived solely from intravenous therapy and he was maintained in positive nitrogen balance. At the end of this time studies of plasma volume were repeated and showed an increase of 600 cc. The protein concentration was 5.10 Gm. By comparison with the original level of 5.06 Gm. this seemed to indicate no improvement, but actually the total circulating proteins increased by 26 per cent (31 Gm.) owing to the increased plasma volume. The patient's appetite greatly improved, and he was able to maintain his caloric intake orally until the time of discharge from the hospital, two weeks later. The protein concentration at this time was above 6 Gm. per hundred cubic centimeters.

Patient 13 was a psychiatric patient who had been admitted to the hospital largely for study. While he was in the hospital, it was found that he had benign prostatic hypertrophy with urinary retention. Urethral drainage was instituted, and shortly thereafter pneumonia developed. Because of the complications the patient's caloric intake had been inadequate, and marked nutritional edema developed. He showed a daily urinary output of nitrogen of 7 to 9 Gm. with an intake of only 2 or 3 Gm. He was given no further feedings for twelve days and was maintained in slightly positive nitrogen balance by intravenous administration of amino acids and dextrose. The protein concentration

15. Fifteen per cent amino acids supplied by Frederick Stearns & Co., Detroit.

rose from 5.30 to 6.43 Gm. per hundred cubic centimeters, and although this seemed to indicate a rather pronounced increase (by comparison with the concentration in the preceding patient), his plasma volume showed a slight decrease. Thus the total circulating proteins had increased by 20 per cent. In this patient, as in the preceding one, diuresis occurred shortly after the amino acids and 10 per cent dextrose were given. At the time therapy was discontinued, the patient was free of edema and able to take an adequate oral diet. It has been thought that the diuretic action was obtained largely from the conversion of amino acids into urea (80 to 90 per cent of the total nitrogen in the urine in these cases is made up of urea nitrogen). Little information could be

TABLE 2.—*Fluid Management in a Case of Bleeding Peptic Ulcer*

Date	Parenteral Intake, Cc.		Oral Intake	Total Output	Hematocrit Value	Plasma Protein Concentration, Gm. per 100 Cc.
	Intravenous	Subcutaneous *				
10/28	950	.....	1,070	1,200	..	4.52
10/29: 1 p. m.	.....	.....	460	600	19	4.10
10 p. m. (operation)	2,000 (blood)	.....	.....	.....	17	3.98
10/30: 2 a. m.	2,450 (blood)	.....	.....	.....	33	5.44
9 a. m.	450 (5% dextrose)	.....	.....	2,235	32	5.20
5 p. m.	.....	.....	.....	.....	34	5.31
10/31	350 (plasma)	2,600	.....	850	33	5.52
11/ 1	1,000 (5% dextrose)	3,000	.....	1,200	30	6.80
11/ 2	2,000	.....	90	2,400	..	....
11/ 3	.....	1,500	550	1,300	30	5.72
11/14	.....	.....	2,300	900	37	5.73

* Five per cent dextrose in physiologic solution of sodium chloride.

gained as to the efficacy of parenteral amino acid therapy by following only the plasma protein concentration. As has been demonstrated in the case of patient 12, a 26 per cent increase occurred in the total circulating plasma protein level when the plasma protein concentration remained the same and the hematocrit value showed a slight increase. An accurate evaluation of such therapy could be obtained only by making studies of nitrogen balance and determinations of plasma volume. Patients 5 and 6 in this series were also treated with intravenous injections of amino acids, and positive nitrogen balance was maintained, but the treatment was continued only until a 12 per cent increase in the total circulating proteins was obtained.

It has also been observed at this hospital that the mortality rate associated with surgical intervention in cases in which medical treatment

of an active bleeding ulcer was unsuccessful is high. Pulmonary complications in two to five days account for most of the deaths. Here again it was found that many of these patients were receiving only 700 to 1,000 cc. of blood at the time of operation and then large quantities of physiologic solution of sodium chloride. The plasma protein concentrations were uniformly low. In table 2 the results are shown for a 55 year old patient who had repeated gastric hemorrhages. The hematocrit value was 17; the plasma protein concentration was 3.98 Gm. per hundred cubic centimeters, and the systolic blood pressure was 50 when gastric resection was undertaken. The patient was given 4,450 cc. of blood and 350 cc. of plasma during the first forty-eight hours postoperatively and 1,800 cc. of physiologic solution of sodium chloride and 1,250 cc. of 5 per cent dextrose. His convalescence was entirely uneventful, and he was discharged fifteen days after operation.

COMMENT

From the cases presented in table 1 it can be seen that in patients who have shown a moderate loss of weight and a diminished intake of food and fluid severe dehydration may exist even though vomiting has not occurred or has been minimal. Also evidence has been given that normal hematocrit values (red blood cell counts and hemoglobin concentrations) and plasma protein concentrations may be obtained when dehydration is accompanied by malnutrition.

It should be kept in mind that patients who have diminished total circulating plasma proteins are likely to have in addition a deficit in tissue proteins in the liver and other organs. This is in keeping with the fact that a negative nitrogen balance exists. Any replacement therapy should be employed, therefore, with the purpose of restoring the entire protein deficit of the body and supplying adequate calories so that the body will no longer derive energy from the breakdown of its own tissues.

In recent years much has appeared in the literature concerning the role of hypoproteinemia in patients with wound dehiscence.[16] Since protein synthesis occurs at the site of a healing wound and the amino acids are the structural units of tissue proteins, it is reasonable to believe that the availability of the needed amino acids is of primary importance. Thus it would appear more logical to associate wound disruption with the presence and the extent of negative nitrogen balance (catabolism of body proteins) rather than solely with the concentration of plasma

16. Whipple, A. O.: Address of President: Critical Latent or Lag Period in Healing of Wounds, Ann. Surg. **112**:481-488, 1940. Hartzell, J. B.; Winfield, J. M., and Irvin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, J. A. M. A. **116**:669-674 (Feb. 22) 1941.

protein. For example, the wound of patient 12 disrupted when the concentration of protein was above 6 Gm. per hundred cubic centimeters and the catabolic process was probably at its maximum. Later several persistent decubiti healed rapidly and a severe lesion of the mouth healed when the plasma protein concentration was around 5 Gm. per hundred cubic centimeters and the body was receiving adequate calories and proteins so that a relatively normal anabolic process existed. This rapid healing has also been noted in treating similar patients by repeated transfusions of plasma.

Patients with malnutrition should receive from 50 to 80 Gm. of nutritionally adequate protein daily and sufficient total calories to protect this. It is naturally important that when fluids must be administered parenterally dextrose be given in adequate amounts so that proteins will not be metabolized solely for body energy but rather be spared so that the constituent amino acids may enter into the synthesis of other tissue proteins. Since it is impractical to administer 1,000 cc. of plasma daily (containing approximately 70 Gm. of protein), a preparation containing amino acids more or less in the proportion in which they occur in a biologically complete protein (for example hydrolysate of casein) would seem to be a likely substitute. At the University Hospitals of Cleveland such a product has been employed without any apparent ill effects. Patients have been maintained in positive nitrogen balance when their sole source of nitrogen has been 15 per cent amino acids given intravenously. The only difficulty encountered has been in supplying adequate amounts of dextrose along with the amino acids. Such a procedure is not difficult for two or three days, but when 10 per cent dextrose is employed to increase the caloric intake thrombosis of veins frequently occurs after twenty-four to seventy-two hours. Intrasternal injections as employed by Tocantins [17] might offer a solution to this problem.[17a] Naturally oral feedings or orojejunal tube [18] feedings would be the most physiologic and desirable method, but these were possible for only a few of the patients presented. Furthermore, supplementary intravenous therapy is frequently advantageous for patients with restricted oral feedings.

Certain rules,[19] employing the plasma chloride concentration, have been advocated to guide the clinician in treating patients who are

17. Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the Circulation Via the Bone Marrow: Technic and Results, Surg., Gynec. & Obst. **73**:281-287, 1941.

17a. Since acceptance of this paper intrasternal administration of amino acids has been carried out on 1 patient with satisfactory results.

18. Stengel, A., Jr., and Ravdin, I. S.: The Maintenance of Nutrition in Surgical Patients with a Description of the Orojejunal Method of Feeding, Surgery **6**:511-519, 1939.

19. Coller, F. A., and Maddock, W. G.: Water and Electrolyte Balance, Surg., Gynec. & Obst. **70**:340-354, 1940.

dehydrated. Such methods would naturally be of great advantage if practical; often however, they give the physician a false sense of security. For example, a low plasma chloride level may occur with dehydration, but it alone gives one no idea as to how much physiologic solution of sodium chloride can be safely administered. As already pointed out, the total circulating plasma proteins would be the only index of the amount which could be safely tolerated. Coller and Maddock [19] pointed out that the thoughtless use of physiologic solution of sodium chloride is definitely harmful, especially to the sick surgical patient. From experimental work on animals [20] and from clinical observations, it is believed that a state of dehydration may frequently occur which is not quantitatively demonstrable by the plasma chloride level, the hematocrit value or the plasma protein concentration. On the other hand, it is known also that if the fluid lost has the same electrolyte pattern (quantitatively and osmotically) as plasma the concentrations of sodium and chloride in the plasma may be normal when the body is in great need of physiologic solution of sodium chloride.

As McIver and Gamble [21] stated in 1928:

> . . . Hepatic duct bile and fluid derived from the intestinal mucosa contain approximately the same amount of fixed base and chloride ion as does plasma. Loss of this fluid will cause a reduction of the volume of the blood plasma and of interstitial fluid but should not alter the plasma chloride (or bicarbonate) concentrations.

Thus they concluded that:

> . . . A point of great practical importance to be derived from this is that it is entirely incorrect to regard the plasma chloride concentration as an index of the degree of dehydration and of the extent to which replacement by salt solution is required.

Gamble and Ross [22] in 1925 brought out the fact that the loss of sodium rather than of the chloride ion is the significant factor in determining the extent of dehydration, since quantitatively sodium is the chief cation of the extracellular fluid and since the loss of chloride ion is compensated for by a corresponding increase in bicarbonate.

Data [20b] from our laboratory showed that animals which were not given food and water by mouth for three to seven days showed plasma

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20. (*a*) Mellors, R. C.; Muntwyler, E.; Mautz, F. R., and Abbott, W. E.: Changes of the Plasma Volume and "Available (Thiocyanate) Fluid" in Experimental Dehydration, J. Biol. Chem. **144**:785-793 (Aug.) 1942. (*b*) Abbott, W. E.; Mellors, R. C., and Muntwyler, E.: Fluid, Protein and Electrolyte Alterations in Experimental Intestinal Obstruction, Ann. Surg. **117**:39-51 (Jan.) 1943.

21. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, J. A. M. A. **91**:1589-1592 (Nov. 24) 1928.

22. Gamble, J. L., and Ross, S. G.: The Factors in Dehydration Following Pyloric Obstruction, J. Clin. Investigation **1**:403-421, 1925.

volumes decreased by 15 to 30 per cent and still had plasma chloride levels of 110 to 120 milliequivalents per liter.

The hematocrit values and the protein concentrations in certain cases may be within the normal range when the total circulating red blood cells or the total amount of plasma protein is greatly decreased (table 1). It has been pointed out by Scudder [23] that the hematocrit value might be confusing in cases of dehydration because of anemia, but little has been said about the total circulating amount of plasma protein or the protein concentration. In 1927, however, Peters [24] did state that conditions that cause malnutrition frequently lead also to dehydration, and the latter by producing hemoconcentration may mask the reduction in the plasma protein level. In this article he also stated that the plasma protein concentration of a patient with carcinoma of the stomach fell from 5.87 to 4.69 Gm. per hundred cubic centimeters after the administration of a solution of sodium chloride. Because of the chronic course of patients with carcinoma of the stomach or the esophagus or with pyloric stenosis due to ulcer and of some with intestinal obstruction, the effects of malnutrition and dehydration are frequently underestimated. It would therefore seem that, while serial hematocrit and protein determinations are of value, more thought and attention should be given the total circulating levels.

In the aforementioned patients and in approximately 15 other such patients a marked difference was noted in the convalescent period between those who were treated carefully with plasma, blood and physiologic solution of sodium chloride and those who were given fluids and transfusions without the same consideration. In almost every instance an uncomplicated postoperative course was experienced when careful studies of fluid balance were carried out.

It is apparent that this series of cases is not large, but from these and from other cases which have been followed the conclusions seem justified.

SUMMARY

From the cases presented it is evident that the hematocrit value and the plasma protein concentration may be near normal even when a relatively large deficit in the total number of red blood cells or the total circulating plasma protein exists. Thus, dehydration may be severe when a normal hematocrit value, plasma chloride level or protein con-

23. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

24. Peters, J. P.; Wakeman, A. M., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition, J. Clin. Investigation **3**:491-495, 1927.

centration is present, and hence these determinations are of limited usefulness and may even be confusing, especially if serial levels are not obtained.

The use of large amounts of physiologic solution of sodium chloride (2,500 to 7,000 cc.) postoperatively in malnourished patients to counteract or prevent dehydration may provoke serious complications (pulmonary edema, atelectasis and bronchopneumonia).

The total circulating plasma proteins frequently fall to a level of clinical importance (from 6 to 50 per cent below normal in the series of patients presented). Several observations would seem to indicate that dehiscence or healing of wounds would bear a much closer relation to catabolism or anabolism of proteins than to the concentration of proteins in the plasma.

In the treatment of such conditions it seems desirable to replenish not only the plasma proteins but also the tissue proteins. If adequate calories cannot be consumed orally, intravenous or intrasternal alimentation should be resorted to.

Amino acids can be employed parenterally as the only source of nitrogen to maintain positive nitrogen balance, and when adequate amounts are given along with sufficient calories, an increase in the total circulating plasma proteins can be obtained.

Western Reserve University School of Medicine.
Poliomyelitis Laboratory, Johns Hopkins University.

AN ANATOMIC STUDY OF VENOUS VARIATIONS AT THE FOSSA OVALIS

THE SIGNIFICANCE OF RECURRENCES FOLLOWING LIGATIONS

S. THOMAS GLASSER, M.D.
NEW YORK

Although this paper primarily concerns itself with the variations of the tributaries of the vena saphena magna at the saphenofemoral junction, the obvious application of this research to ligation of veins and to recurrences after treatment of varicose veins is apparent. The unequivocal value of high ligation is established. The popularity of this procedure and its widespread use, particularly by surgeons unfamiliar with the field of vascular surgery, account for the not uncommon failures and recurrences. A lack of knowledge of the anatomy of the venous drainage of the lower extremity is probably the greatest single cause of poor results. In view of the exploratory nature of the operations required because of common variations, it would not be amiss at this point to emphasize the fact that ligation of the saphenous vein is not an office procedure.

The material in this communication is based on the dissection in the fossa ovalis region of 100 lower extremities (50 cadavers).[1] The great number of variations should not be considered unusual, because it is known that venous patterns throughout the body are generally inconstant. Numerous variations have also been observed wherever an opening similar to the fossa ovalis is present—note the abnormalities in the popliteal and other similar regions. The striking finding in these dissections was the frequent occurrence of accessory saphenous and prominent lateral superficial femoral veins. This is decidedly at variance with the usual textbook picture depicting these as small, multiple veins draining into the vena saphena magna far below the fossa ovalis.[2] This venous

From the Department of Anatomy and Surgery, New York Medical College, Flower and Fifth Avenue Hospitals and Metropolitan Hospital.

1. Glasser, S. T.: Variations of the Tributaries of the Saphena Magna at the Sapheno-Femoral Junction: Abstract of Demonstration, Anat. Rec. **82**:93 (March 25) 1942.

2. (*a*) Piersol, G. A.: Human Anatomy, ed. 4, Philadelphia, J. B. Lippincott Company, 1913, pp. 916-917. (*b*) Spalteholz, H. W.: Atlas of Human Anatomy, edited by L. F. Barker, ed. 4, Philadelphia, J. B. Lippincott Company, 1923, vol. 2. (*c*) Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 22, Philadelphia, Lea & Febiger, 1930, pp. 734-735. (*d*) Deaver, J. B.: Surgical Anatomy, Philadelphia, P. Blakiston's Son & Co., 1903, vol. 3, p. 557. (*e*) Quain,

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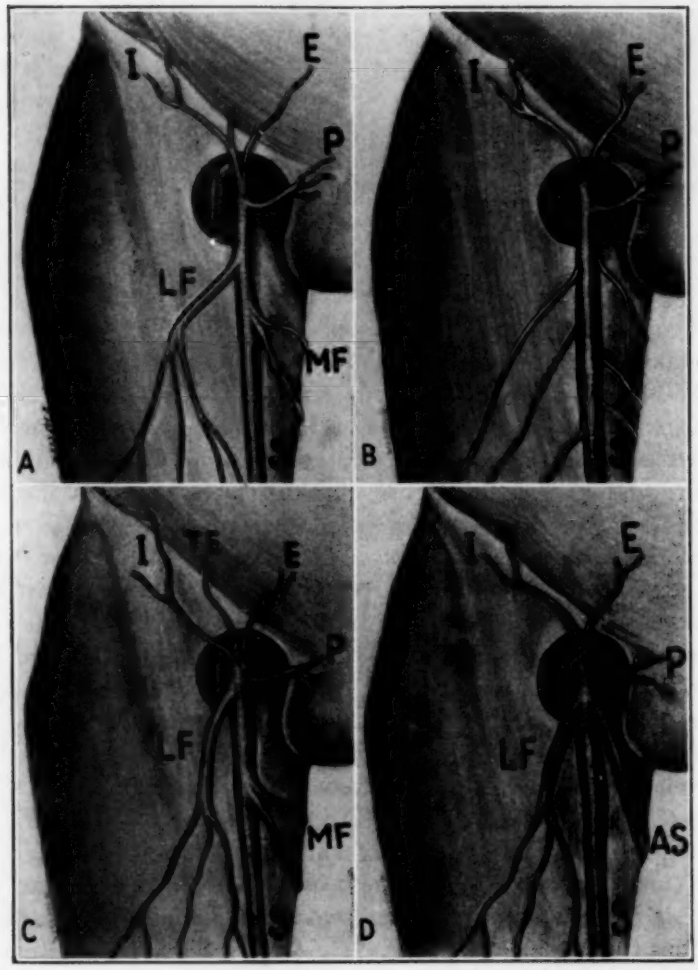

Fig. 1.—*A*, Average "textbook" diagram of venous drainage at fossa ovalis. Incidence 37 per cent. *B*, Multiple divisions of the medial and lateral femoral veins of small caliber. Incidence 6 per cent. *C*, The large lateral superficial femoral vein drains into the fossa ovalis. The inconstant thoracoepigastric vein drains into the vena saphena magna instead of into the femoral vein. Incidence 2 per cent. *D*, The lateral superficial femoral and the accessory saphenous vein drain into the fossa ovalis. Incidence 2 per cent. Abbreviations used in this and in the following illustrations are as follows: *I*, superficial circumflex iliac vein; *E*, superficial epigastric vein; *P*, superficial external pudendal vein; *LF*, lateral superficial femoral vein; *MF*, medial superficial femoral vein; *AS*, accessory saphenous vein; *SS*, double saphenous vein; *S*, vena saphena magna; *TE*, thoracoepigastric vein; *F*, femoral vein.

J.: Elements of Anatomy, ed. 9, London, Longmans, Green & Co., 1882, vol. 1, pp. 519-520. (*f*) Cunningham, D. J.: Cunningham's Text Book of Anatomy, edited by J. C. Brash and E. B. Jamieson, ed. 7, London, Oxford University Press, 1937, pp. 1270-1272. (*g*) Ochsner, A., and Mahorner, H.: Varicose Veins, St. Louis, C. V. Mosby Company, 1939.

pattern, occurring in only 37 per cent of our series, is illustrated in figure 1 *A*. If figures 1 *B* and 4 *D* are added to the preceding group, the total number of cases in which "insignificant" medial and lateral superficial femoral veins were present would be 44 per cent. In other words, more than 50 per cent of the dissections illustrated prominent superficial

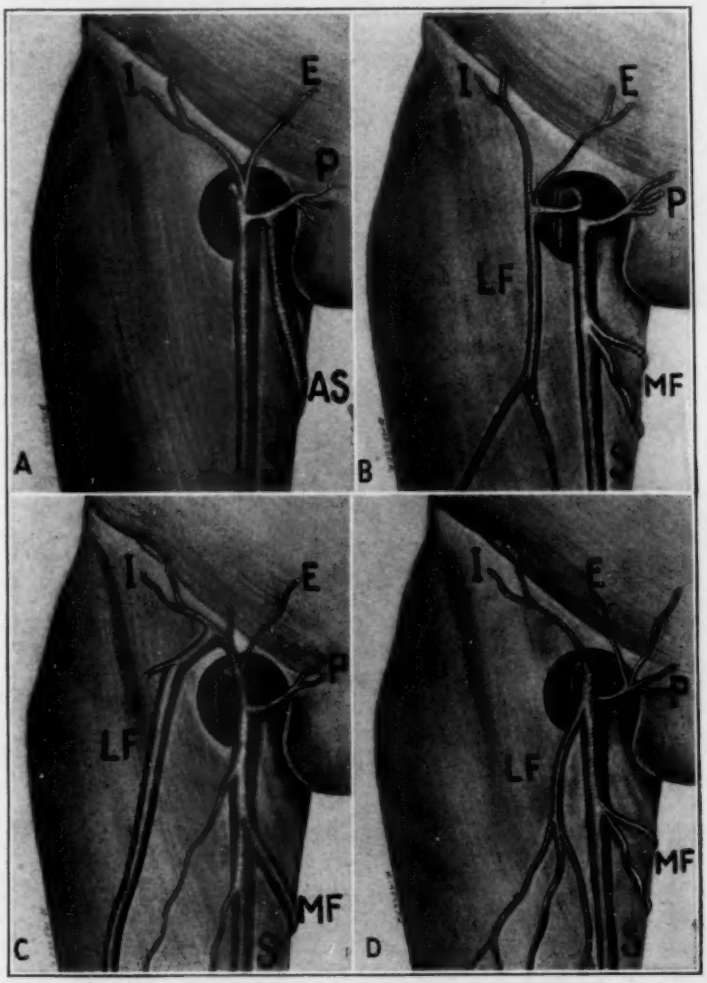

Fig. 2.—*A*, The accessory saphenous vein forms a common stem with the superficial external pudendal vein before joining the vena saphena magna. Incidence 6 per cent. *B*, A common trunk formed by the lateral superficial femoral, superficial circumflex iliac and superficial epigastric veins drains into the fossa ovalis. Incidence 9 per cent. *C*, A common trunk formed by the lateral superficial femoral and the superficial circumflex iliac vein drains into the fossa ovalis. Incidence 9 per cent. *D*, The superficial epigastric and the superficial external pudendal vein form a common trunk. A large lateral superficial femoral vein is present. Incidence 2 per cent.

femoral veins.[28] The significance of these so-called variations becomes of major importance when an analysis of recurrences is considered. The higher tributaries are of less importance as causes of failure in treatment, except in those infrequent instances in which the superficial femoral

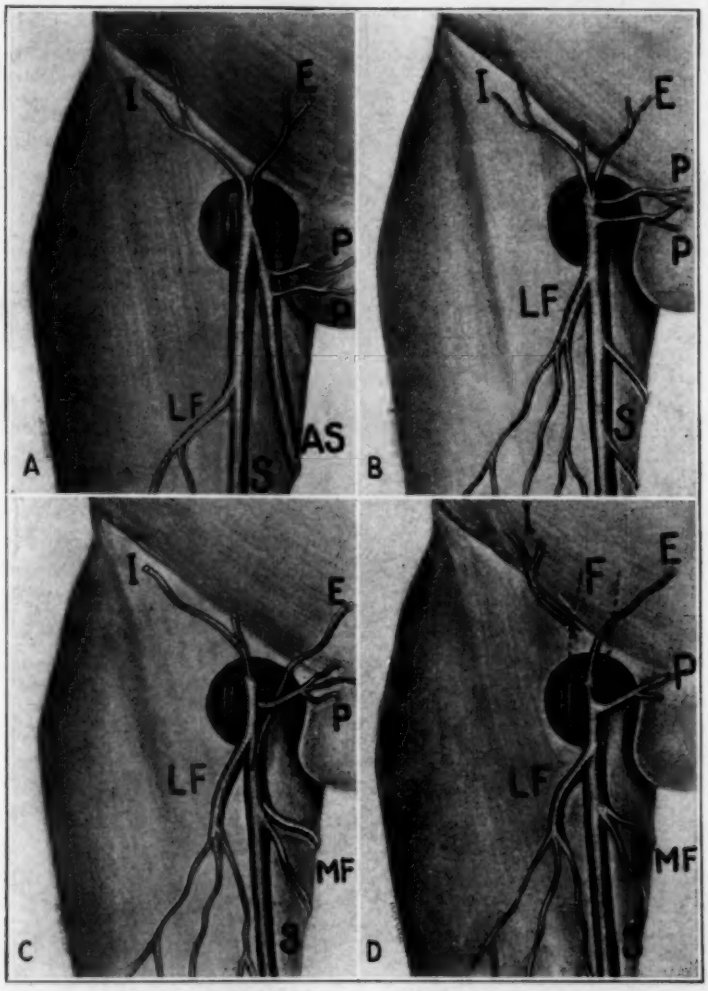

Fig. 3.—*A*, An accessory saphenous vein is present. Note the drainage of double superficial external pudendal veins. Incidence 1 per cent. *B*, Double superficial external pudendal veins drain into the fossa ovalis. Incidence 3 per cent. *C*, The superficial epigastric vein drains into the vena saphena magna below the fossa ovalis. Incidence 3 per cent. *D*, The superficial circumflex iliac vein drains into the femoral vein. Incidence 1 per cent.

veins form separate junctions with the pudendal, circumflex iliac or epigastric veins (figs. 2 *A*, 2 *B*, 2 *C*, 4 *B* and 5 *A*). A double saphenous

vein was found in only 3 per cent of the specimens (fig. 5 *B*). The incidence of direct drainage into the femoral vein of the higher tributaries collectively or singly was 16 per cent (figs. 3 *D*, 4 *A*, 4 *B*, 4 *C*, 4 *D* and 5 *A*). In one instance (fig. 5 *C*) the vena saphena magna was found to pierce the deep fascia and join the femoral vein about 1 inch (2.5 cm.)

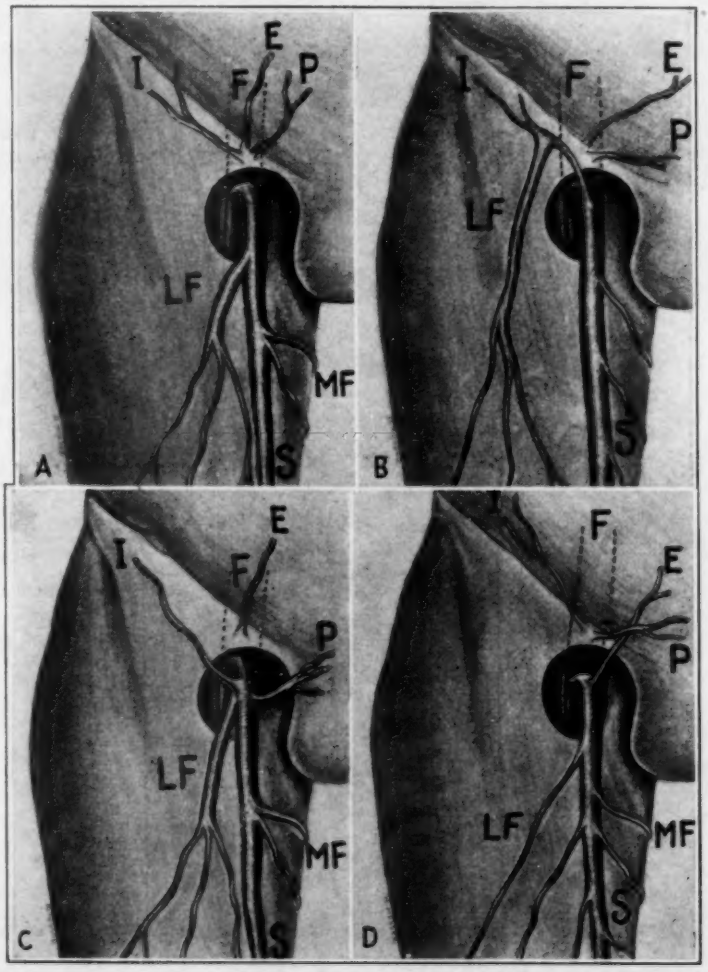

Fig. 4.—*A*, All high collateral veins drain directly into the femoral vein. Incidence 6 per cent. *B*, The lateral femoral and the superficial circumflex iliac vein form a common trunk. The other high collateral veins drain directly into the femoral vein. Incidence 1 per cent. *C*, The lateral femoral vein drains into the fossa ovalis. The superficial epigastric vein drains directly into the femoral vein. Incidence 6 per cent. *D*, Note the small caliber multiple medial and lateral superficial femoral veins. The superficial circumflex iliac and the superficial external pudendal vein drain directly into the femoral vein. Incidence 1 per cent.

below the fossa ovalis. This is a rare occurrence and has been described by Ochsner and Mahorner.[28]

The clinical application of this study to the patients with recurrences reoperated on in our institution has not been thoroughly studied. Such a review is intended for a subsequent report. Most patients for whom a

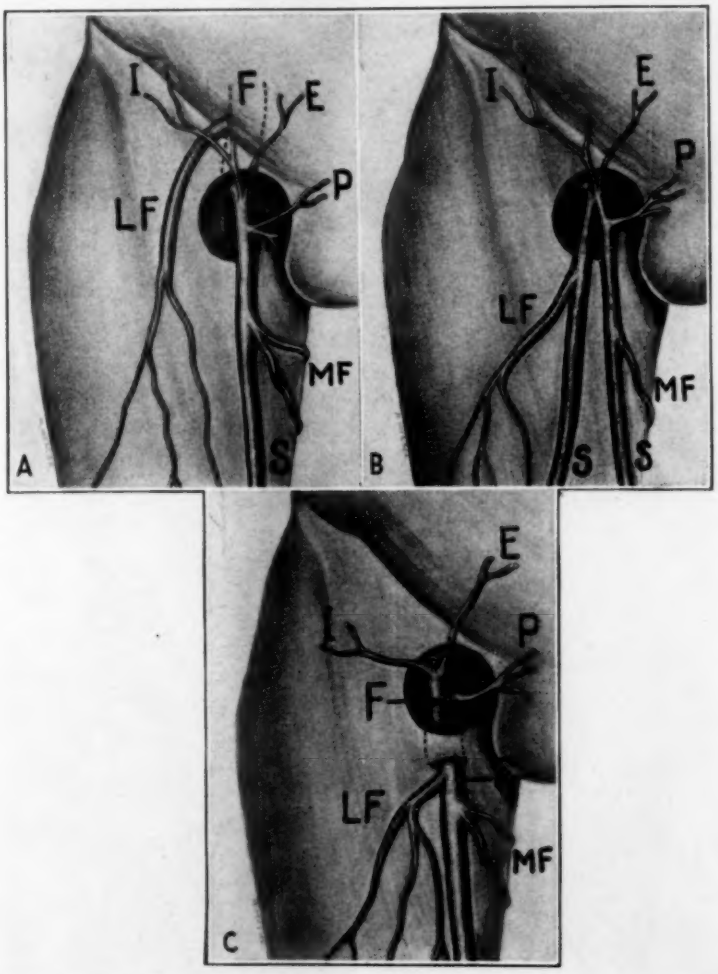

Fig. 5.—*A*, The lateral superficial femoral vein drains directly into the femoral vein. Incidence 1 per cent. *B*, A double vena saphena magna with joining at the fossa ovalis. Incidence 3 per cent. *C*, The saphena magna pierces the deep fascia to enter the femoral vein about 1 inch below the fossa ovalis. Incidence 1 per cent.

secondary operation was deemed necessary declined it. In those patients who permitted a second exploration, the presence of a patent medial (accessory) or a lateral superficial femoral vein was noted. There were

no examples of recurrence due to failure in ligation of the higher tributaries at the time of the primary operation. A finding of interest was the complaint of persistent pain which was relieved after the secondary operation. The mechanism of this finding is problematic, but it may possibly be due to reflex venospasm.

Another observation of importance is the dislocation in position and course of the tributaries in the presence of enlarged saphenous glands. Operative manipulation in these cases was found to be especially painful. The hypertrophied glands nearly always displaced the vena saphena magna medially.

Over 500 ligations have been performed in our peripheral vascular clinic. A proper follow-up of these patients will be made to determine the value of the aforementioned statements.

SUMMARY

An anatomic study of 100 dissections of the lower extremity in the region of the fossa ovalis with particular attention to the variations of the tributaries of the vena saphena magna is discussed.

Variations of the superficial femoral veins are probably the chief causes of recurrences following faulty primary ligations for the treatment of varicose veins.

The presence of pain in cases with recurrence seems to be frequent.

The presence of hypertrophied saphenous glands causes dislocation of the tributaries and also makes operative manipulation painful.

INTRAVENOUS USE OF VITAMIN K_1 OXIDE

WILLIAM A. DAVIS, M.D.

HOWARD A. FRANK, M.D.

ALFRED HURWITZ, M.D.

AND

ARNOLD M. SELIGMAN, M.D.

BOSTON

The clinical importance of parenteral therapy with vitamin K has become well established. The most prolonged improvements in prothrombin clotting time so far reported have followed the intravenous administration of either synthetic vitamin K_1 or 2-methyl-1,4-naphthoquinone (menadione). The chemical reactivity and the toxicity of menadione as described by Fieser [1] make it less desirable for general use than vitamin K_1. A single dose of one of these drugs can restore and maintain normal blood prothrombin levels for periods as long as two or three weeks.[2] Some inconvenience is caused by their lack of solubility in water and their sensitivity to ultraviolet rays. This has led to the continued use of water-soluble preparations; the effects of these are of much shorter duration, so that repeated injection is required for prolonged effect.

After the synthesis of vitamin K_1, Fieser [3] postulated that this light-sensitive vitamin probably did not exist as the quinone in the green alfalfa leaf from which it had been isolated. He suggested that vitamin K_1 may be present in the green leaf as its oxide. Tishler, Fieser and Wendler [4] synthesized the oxide and found it to be readily reducible

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From the Medical Service, Peter Bent Brigham Hospital, and the Surgical Service, Beth Israel Hospital.

This investigation was aided by a grant from the Proctor Fund, Department of Medicine, Harvard Medical School.

1. Fieser, L. F.: Ann. Int. Med. **15**:648, 1941. According to J. V. Scudi (Proc. Soc. Exper. Biol. & Med. **50**:16-17, 1942), when menadione is added to whole, unlaked blood it causes a pronounced formation of methemoglobin, and the drug is rapidly converted to some other substance, with marked loss in antihemorrhagic activity.

2. (*a*) Frank, H. A.; Hurwitz, A., and Seligman, A. M.: New England J. Med. **221**:975, 1939. (*b*) Seligman, A. M.; Hurwitz, A.; Frank, H. A., and Davis, W. A.: Surg., Gynec. & Obst. **73**:686, 1941.

3. Fieser, L. F.: J. Am. Chem. Soc. **61**:2559, 1939; footnote 1.

4. Tishler, M.; Fieser, L. F., and Wendler, N. L.: J. Am. Chem. Soc. **62**: 2866, 1940.

to the hydroquinone of vitamin K_1. Fieser, Tishler and Sampson [5] found the oxide to be three times as stable as the quinone on exposure to ultraviolet light and "hardly distinguishable" from the vitamin itself in assays on chicks. These workers were impressed with a similarity in properties between the synthetic oxide and a colorless fraction isolated from alfalfa by Fernholz, Ansbacher and co-workers.[6]

Because of the ease of preparation of the oxide from vitamin K_1 and its stability to ultraviolet rays, it was felt that the substance merited clinical trial. Although the oxide, like the vitamin itself, is not soluble in water, it was found that a stable suspension of therapeutic doses suitable for intravenous injection could be made in volumes as small as 10 cc. This seemed to increase the likelihood that the oxide would be a more generally useful agent for intravenous therapy with vitamin K. This paper reports the intravenous use of synthetic vitamin K_1 oxide.[7]

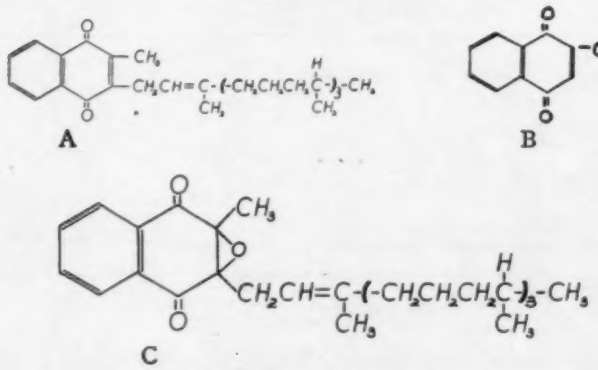

Chart 1.—Structural formulas for: *A*, vitamin K_1; *B*, 2-methyl-1,4-naphthoquinone (menadione); *C*, vitamin K_1 oxide.

METHOD

Vitamin K_1 oxide can be prepared in liter volume for intravenous administration as a colloidal suspension by the method already described for vitamin K_1.[2] However, it was found that stable suspensions of the oxide in solutions of dextrose or sodium chloride (remaining homogeneous for at least two months) could be made more concentrated than in the case of vitamin K_1, a preliminary announcement of this finding having been made by Fieser.[1] It was found convenient to draw 10 mg. of the oxide dissolved in 3 cc. of alcohol into a syringe containing 10 cc. of

5. Fieser, L. F.; Tishler, M., and Sampson, W. L.: J. Biol. Chem. **137**:659, 1941.

6. Ansbacher, S.; Fernholz, E., and MacPhillamy, H. B.: Proc. Soc. Exper. Biol. & Med. **42**:655, 1939. Fernholz, E.; Ansbacher, S., and Moore, M. L.: J. Am. Chem. Soc. **61**:1613, 1939.

7. Provided by Prof. Louis F. Fieser, Harvard University.

sterile physiologic solution of sodium chloride immediately before injection. For sterilization sealed ampules of the oxide in alcohol were autoclaved before being mixed with sterile solution of sodium chloride. No untoward reaction followed the administration of these suspensions.

The prothrombin determination of Quick[8] was employed. The normal range was thirteen and a half to seventeen seconds.

RESULTS

Case 1.—M. M., a 45 year old woman with a past history of injury of the common duct, choledochoduodenostomy and intermittent jaundice, chills and fever of two years' duration, entered the hospital for relief of obstruction of the common duct. Examination revealed jaundice and a markedly enlarged liver. Laboratory data on admission were as follows: The urine contained bile. The stools were brown. A guaiac test gave negative results. The red blood cell count was 4,300,000, the hemoglobin content 70 per cent and the white blood cell count 10,400, with 72 per cent polymorphonuclear leukocytes. The nonprotein nitrogen content of the blood was 29 mg. per hundred cubic centimeters. The icterus index was 49.

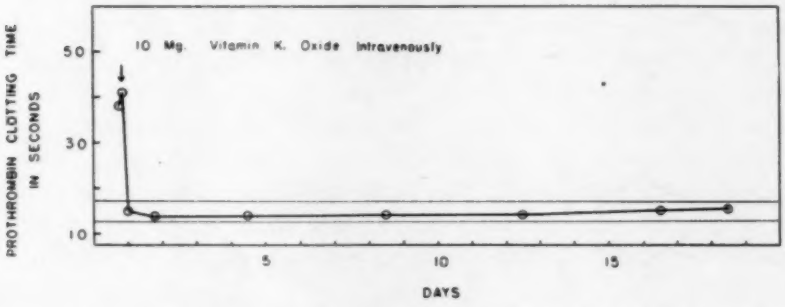

Chart 2.—Course of prothrombin clotting times for patient in case 1.

The protein content of the serum was 7.7 Gm. per hundred cubic centimeters, with albumin 3.7 Gm. and globulin 4 Gm. The cholesterol content was 430 mg. per hundred cubic centimeters. The blood diastase content was normal. The bleeding time was three and a half minutes (Duke test); clotting time, fourteen minutes (test tube); the prothrombin clotting time, ninety seconds.

On the day following admission to the hospital the patient received 6 mg. of vitamin K_1 oxide intravenously. When laparotomy was performed a week later, the bleeding time was six minutes and the prothrombin clotting time sixteen and a half seconds. Complete obliteration of the lower portion of the common duct was found. Choledochoduodenostomy was reestablished after mobilization of the proximal segment; external drainage was afforded, and biopsy of the liver was done. Convalescence was uneventful, and the patient was discharged from the hospital with the T tube clamped on the fifteenth postoperative day. No unusual bleeding was noted at operation or thereafter. Following discharge the patient's jaundice

8. Quick, A. J.: Nature of Bleeding in Jaundice, J. A. M. A. **110**:1658 (May 14) 1938.

disappeared and her liver diminished in size. The biopsy of the liver revealed acute hepatitis and obstructive biliary cirrhosis.

The course of the prothrombin clotting times is shown in chart 2. The rapid response and the prolonged action following a single dose of the oxide in this patient with biliary obstruction and hepatitis are shown.

CASE 2.—H. B., a 59 year old woman with a past history of radical mastectomy for carcinoma six years before, entered the hospital because of the gradual development of jaundice, malaise and nausea in the two months preceding admission. Examination revealed extreme jaundice, bleeding excoriations of the skin, numerous ecchymoses, ascites, a large, nontender liver and bloody discharge from the rectum. The left breast was absent, and there was a nodule in the mastectomy scar. Laboratory data on admission were as follows: The urine contained bile. The red blood cell count was 3,500,000, the hemoglobin content 75 per cent and

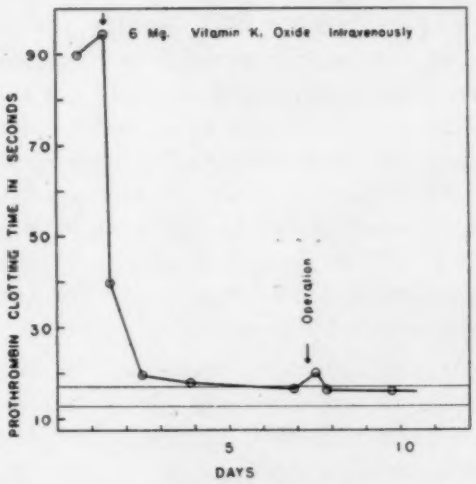

Chart 3.—Course of prothrombin clotting times for patient in case 2.

the white blood cell count 6,000 with 85 per cent polymorphonuclear leukocytes. The nonprotein nitrogen content of the blood was 36 mg. per hundred cubic centimeters. The protein content of the serum was 5.8 Gm. per hundred cubic centimeters, with albumin 2.8 Gm. and globulin 3 Gm. The icterus index was 149. The stools were gray or black. A guaiac test gave positive results. The prothrombin clotting time was thirty-eight seconds. There was roentgen evidence of pulmonary metastases, and tumor cells were found in the paracentesis fluid. One hour after admission the patient received 10 mg. of vitamin K_1 oxide intravenously. All evidence of generalized bleeding disappeared. The patient became progressively worse and died on the twenty-first day of hospitalization. Permission for postmortem examination was not obtained.

The course of the prothrombin clotting time is shown in chart 3. A rapid and prolonged effect from a single dose of the oxide was obtained in this patient with obstructive jaundice from metastatic carcinoma. The more rapid response to the vitamin in this case as compared with that in the previous one is probably attributable to a less severe degree of hepatic impairment.

SUMMARY

Vitamin K_1 oxide, synthesized by Fieser and co-workers and shown to be three times as stable as vitamin K_1 to ultraviolet rays, has been tested clinically for the first time.

A convenient method for preparing the synthetic vitamin K_1 oxide for intravenous administration is described.

A single intravenous dose of vitamin K_1 oxide was found to produce the rapid response and the prolonged action noted with vitamin K_1.[2b]

Merck & Co., Inc., provided a large supply of vitamin K_1 oxide.

330 Brookline Avenue.

CONCENTRATION OF PROCAINE IN THE CEREBROSPINAL FLUID OF THE HUMAN BEING AFTER SUBARACHNOID INJECTION

THIRD REPORT

H. KOSTER, M.D.
BROOKLYN

Elsewhere my associates and I [1] have reported on the concentration of procaine in the subarachnoid space during spinal anesthesia in patients in the Trendelenburg position. The reports were based on the analysis of samples taken at various intervals of time from three groups of adult patients, at the site of injection, from a site three interspaces above and from the cisterna magna. The first group of 122 patients received 150 mg. of procaine hydrochloride dissolved in 3.5 cc. of cerebrospinal fluid; the second group of 156 patients received 300 mg. dissolved in 3.5 cc., and the third group of 143 patients received 300 mg. dissolved in 7 cc. All injections were made between the second and the third lumbar vertebra, and the patients were immediately placed in the Trendelenburg position. After this samples were taken.

At the moment of injection the concentration at the site of injection is at its maximum, namely, the concentration of the injected fluid (43 mg. per cubic centimeter). This falls rapidly in the first few minutes. At the moment of injection the concentration of procaine three interspaces above the site of injection is 0, but it rises rapidly in the first four minutes. The maximum concentration here is never above 4 mg. per cubic centimeter, and at no moment does it equal the level at the site of injection. From then on the concentrations at the site of injection and three interspaces above decrease at approximately the same rate, and at no time is the concentration in the dorsal region as great as in the lumbar. The highest concentration in the cisterna is never greater than 0.21 mg. and frequently less than 0.02 mg. per cubic

From the Richard Morton Koster Research Laboratory.

1. (*a*) Koster, H.; Shapiro, A., and Leikensohn, A.: Spinal Anesthesia: Procaine Concentration Changes at the Site of Injection in Subarachnoid Anesthesia, Am. J. Surg. **33**:245-248 (Aug.) 1936; (*b*) Concentration of Procaine in the Cerebrospinal Fluid of the Human Being After Subarachnoid Injection, Arch. Surg. **37**:603-608 (Oct.) 1938. (*c*) Koster, H.; Shapiro, A., and Warshaw, R.: Concentration of Procaine in the Cerebrospinal Fluid of the Human Being After Subarachnoid Injection, ibid. **39**:97-103 (July) 1939.

centimeter. Comparative analysis of these data did not support the assumption of many authors [2] that the Trendelenburg position causes concentrated solutions of procaine hydrochloride to flow down to the cisterna magna as do colored solutions in inanimate models.

It is obvious that the information obtained regarding the concentration of procaine in patients under the circumstances just described could be used as a standard for comparison. It was then deemed advisable to repeat the experiment with patients in the Fowler position to determine whether the concentration curves would be significantly changed by the change in posture.

METHOD

One hundred and twenty-eight adult patients received an injection of procaine hydrochloride dissolved in 3.5 cc. of cerebrospinal fluid at the interspace between the second and the third lumbar vertebra. The patients were then placed in the Fowler position at angles of 10 degrees. At different intervals after the injection, samples of 1 cc. of cerebrospinal fluid were withdrawn from various patients. From a group of 55 patients samples were withdrawn from the site of injection. From another group, of 56 patients, samples were withdrawn three interspaces cephalad. From a third group, of 17 patients, samples were withdrawn from the cisterna magna. The concentration of procaine in these samples was determined in most cases in duplicate or triplicate by the micromethod previously described,[3] with an error not over 10 per cent.

RESULTS

The concentrations of procaine in the spinal fluid at the site of injection, at a site three interspaces above and in the cisterna magna in patients in the Fowler position are shown graphically in charts 1, 2 and 3.

At the moment of injection the maximum concentration at the site of the injection is that of the injected solution (43 mg. per cubic centimeter). This falls rapidly, so that at the end of ten minutes the level of concentration is in the neighborhood of 2 mg. per cubic centimeter. The level of concentration falls slowly thereafter until the anesthesia wears off.

At the moment of injection the level of concentration three interspaces above the site of injection is 0, but it then mounts rapidly in the

2. Pitkin, G. H.: Controllable Spinal Anesthesia, Am. J. Surg. **5**:537-553 (Dec.) 1928. Co Tui, F. W.: Further Studies in Subarachnoid Anesthesia, Anesth. & Analg. **13**:143 (July-Aug.) 1934. Vehrs, A. R.: Problems in the Hydrodynamics of Analgesics in the Subarachnoid Fluid of Man: Diazotized Novocaine in Artificial Dural Sacs, West. J. Surg. **43**:16-32 (Jan.) 1935. Babcock, W. W.: Spinal Anesthesia in Fact and Fancy, Surg., Gynec. & Obst. **59**:94-100 (July) 1934.

3. Koster, H.; Shapiro, A., and Posen, E.: A Micromethod for the Quantitative Determination of Procaine in Cerebrospinal Fluid, J. Lab. & Clin. Med. **21**:1096-1098 (July) 1936.

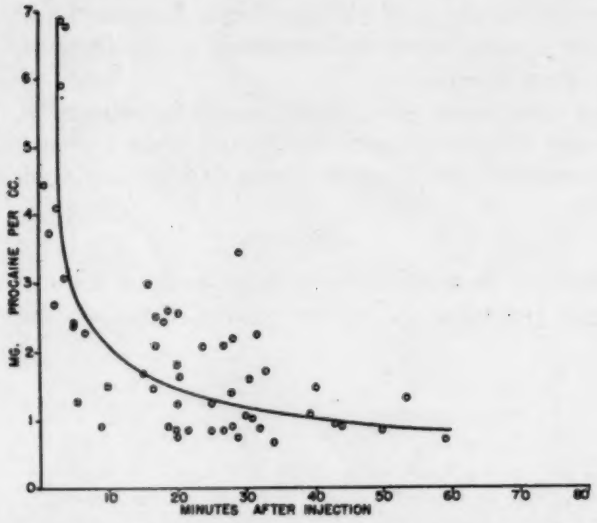

Chart 1.—Concentration of procaine in the cerebrospinal fluid at the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Fowler position.

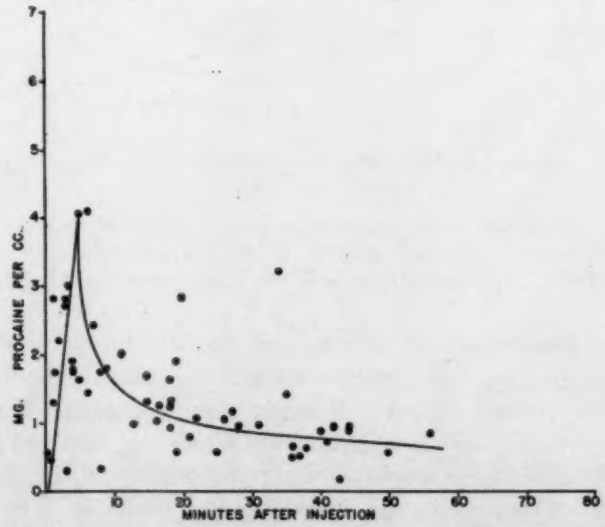

Chart 2.—Concentration of procaine in the cerebrospinal fluid three interspaces above the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Fowler position.

first five minutes to the level of 4 mg. per cubic centimeter. After reaching a peak it falls rapidly for approximately four or five minutes and then more slowly until the anesthesia disappears. At all times, however, the concentration here maintains a slightly lower level than that at the site of injection.

Samples taken from the cisterna magna in patients in the Fowler position never showed concentration values greater than 0.18 mg. per cubic centimeter and frequently less than 0.02 mg. per cubic centimeter.

COMMENT

With patients in a 10 degree Fowler position the cisterna magna is at a higher level than the lumbar portion of the subarachnoid space.

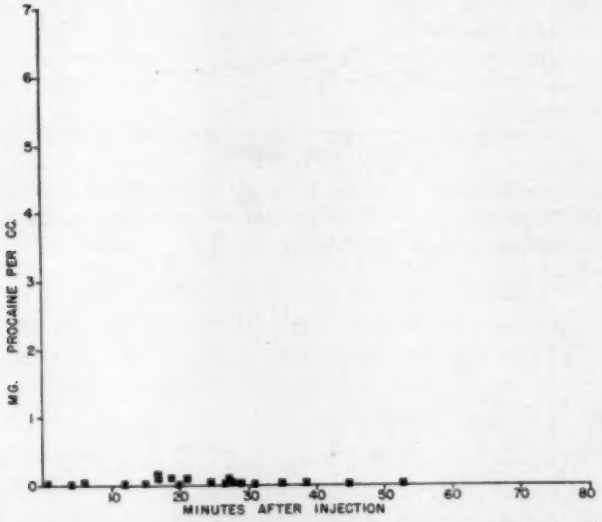

Chart 3.—Concentration of procaine in the cerebrospinal fluid in the cisterna cerebellomedullaris in different patients at various intervals after the injection of the anesthetic. The patients were in the Fowler position.

If the distribution of the injected anesthetic solution is significantly affected by gravity, it might be expected that no anesthetic would be found in the cisterna magna. It might also be expected that the concentration values of samples taken at the site of injection and from a site three interspaces above would vary significantly from samples similarly obtained from patients in the Trendelenburg position. The difference between the two positions is represented by an angle of between 15 and 18 degrees.

In the Fowler position procaine is found in the cisterna magna in small amounts. The values are not significantly different from those

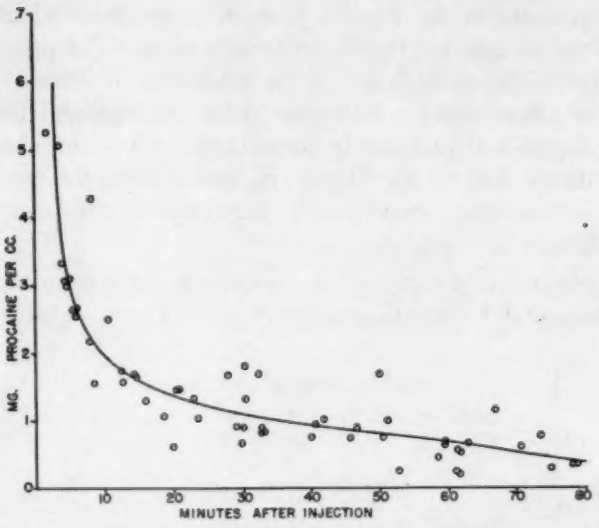

Chart 4.—Concentration of procaine in the cerebrospinal fluid at the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Trendelenburg position.

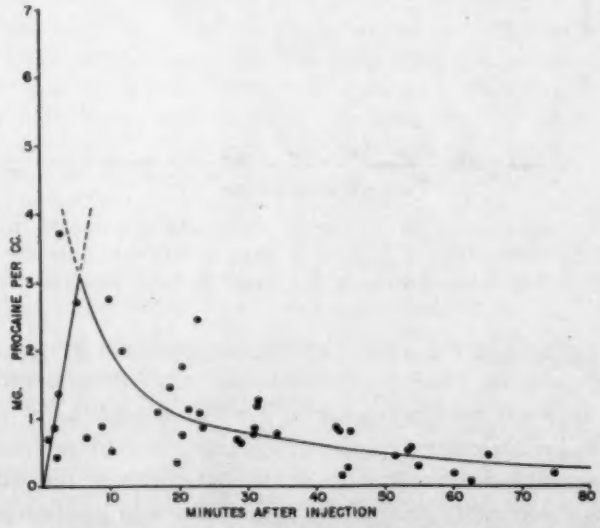

Chart 5.—Concentration of procaine in the cerebrospinal fluid three interspaces above the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Trendelenburg position.

similarly obtained for patients in the Trendelenburg position. Some explanation might be found for the presence of procaine in the cisterna magna in patients in the Fowler position, a presence which serves to contradict the assumption that concentrated solutions of procaine hydrochloride flow to dependent parts of the subarachnoid space as do colored solutions in glass models. However these findings and the existence of similar amounts of procaine in patients in the Trendelenburg position seem to indicate that for the degrees of change from the true horizontal position used in these experiments gravitational displacement of the injected solution is negligible.

For convenience of comparison the data on the concentration of procaine at the site of injection, three interspaces above and in the cisterna

Chart 6.—Concentration of procaine in the cerebrospinal fluid in the cisterna cerebellomedullaris in different patients at various intervals after the injection of the anesthetic. The patients were in the Trendelenburg position.

magna in patients in the Trendelenburg position are graphically reproduced [1b] in charts 4, 5 and 6. It can be seen that there is no significant difference between the concentration curves of patients in the Fowler and in the Trendelenburg position. This seems to indicate that the factors responsible for the spread of the anesthetic in the subarachnoid space are not noticeably affected by such changes in position as occurred in these experiments. It also indicates that within these limits concentrated solutions of procaine hydrochloride do not settle into dependent portions of the subarachnoid space as do colored solutions in inanimate models.

40 Maple Street.